PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

CHOI, Kyu-Pal
824-11, Yeoksam-dong
Kangnam-ku
Seoul 135-080
RÉPUBLIQUE DE CORÉE

Date of mailing (day/month/year) 20 September 2001 (20.09.01)	
Applicant's or agent's file reference PC00010-LG	**IMPORTANT NOTIFICATION**
International application No. PCT/KR00/01047	**International filing date** (day/month/year) 18 September 2000 (18.09.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
LG CHEMICAL LTD. 20, Yoido-dong Yongdungpo-ku Seoul 150-010 Republic of Korea	KR	KR
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
LG CHEM INVESTMENT LTD. 20, Yoido-dong Yongdungpo-ku Seoul 150-010 Republic of Korea	KR	KR
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Idhir BRITEL
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994) 004304237

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

CHOI, Kyu-Pal
824-11, Yeoksam-dong
Kangnam-ku
Seoul 135-080
RÉPUBLIQUE DE CORÉE

Date of mailing (day/month/year) 20 September 2001 (20.09.01)	
Applicant's or agent's file reference PC00010-LG	**IMPORTANT NOTIFICATION**
International application No. PCT/KR00/01047	**International filing date** (day/month/year) 18 September 2000 (18.09.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
LG CHEMICAL LTD. 20, Yoido-dong Yongdungpo-ku Seoul 150-010 Republic of Korea	KR	KR
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
LG CHEM INVESTMENT LTD. 20, Yoido-dong Yongdungpo-ku Seoul 150-010 Republic of Korea	KR	KR
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Idhir BRITEL
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994) 004304237

ATENT COOPERATION TRE TY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 15 May 2001 (15.05.01)	
International application No. PCT/KR00/01047	**Applicant's or agent's file reference** PC00010-LG
International filing date (day/month/year) 18 September 2000 (18.09.00)	**Priority date** (day/month/year) 17 September 1999 (17.09.99)
Applicant KIM, Eunice, Eun-Kyeong et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   05 February 2001 (05.02.01)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Pascal Piriou
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

99-4286

Han Sung International Patent & Law Office

K. P. CHOI　S. J. KIM
E. S. LEE　S. W. RHEE
E. M. BYUN　M. J. PARK
Y. G. LEE　C. S. CHOI
Y. S. KIM　S. J. KIM
B. K. SEO　K. H. PARK
M. K. KIM　J. S. CHO
E. J. KIM　S. Y. LEE

4th Fl., Halla Classic Bldg.
824-11, Yeoksam-Dong,
Kangnam-Ku, Seoul, Korea

Mail : Kang Nam P.O.Box 1793
Seoul 135-080 Korea
Tel : (82-2) 555 - 6888
Fax : (82-2) 555 - 9888
(82-2) 555 - 4958
E-mail : hansung@hsip.co.kr
HomePage : www.hsip.co.kr

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20,
Switzerland

August 20, 2001

By Fax-(41-22) 740 14 35

Re: International Application No. PCT/KR00/01047
International Filing Date : September 18, 2000
Priority Date : September 17, 1999
Applicant : LG CHEMICAL LTD. et al
Agent's File Reference : PC00010-LG

Dear Sirs:

With reference to the above identified international application, LG Chemical Ltd. was the applicant for the purpose of all designated States except the United Staes of America.

We are informing you that the applicant's name was changed from **LG Chemical Ltd.** to **LG Chem Investment Ltd.** on April 3, 2001. The address of the applicant has not been changed.

Changed name : **LG Chem Investment Ltd.**
Address : 20, Yoido-dong, Yongdungpo-ku, 150-010 Seoul, Korea
Nationality : Republic of Korea

We request that the International Bureau of WIPO record the changed name of the applicant and notify all Offices and PCT Authorities concerned of the change of name accordingly. We would appreciate receiving a Notification of the Recording of a Change (Form PCT/IB/306) as quickly as possible. The original of this letter will be sent to you by DHL courier.

Respectfully submitted

Kyu Pal CHOI, Patent Attorney

KPC/BKS

COPY FOR IB

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Artcle 36 and Rule 70)

Applicant's or agent's file reference PC00010-LG	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. **PCT/KR00/01047**	International filing date *(day/month/year)* 18 SEPTEMBER 2000 (18.09.2000)	Priority date *(day/month/year)* 17 SEPTEMBER 1999 (17.09.1999)
International Patent Classification (IPC) or national classification and IPC **IPC7 C07D 261/04, A61K 31/41**		
Applicant [LG CHEMICAL LTD. et al] * LG CHEM INVESTMENT LTD.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demamd	Date of completion of this report
05 FEBRUARY 2001 (05.02.2001)	10 JANUARY 2002 (10.01.2002)
Name and mailing address of the IPEA/KR Korean Intellectual Property Office Government Complex-Daejeon, Dunsan-dong, Seo-gu. Daejeon Metropolitan City 302-701. Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer CHO, Hee Won Telephone No. 82-42-481-5607

Form PCT/IPEA/409 (cover sheet) (July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International aplication No.
PCT/KR00/01047

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed

☐ the description:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☐ the claims:
pages _____ , as originally filed
pages _____ , as amended (together with any statment) under Article 19
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☐ the drawings:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☐ the sequence listing part of the description:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application(under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide** and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained inthe international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disc losure in the international applicationas as filed has been furinshed.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:
☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheet _____

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box(Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed." and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International aplication No.
PCT/KR00/01047

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☐ claims Nos. _____

because:

☒ the said international application, or the said claims Nos. 11
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

Claim 11 relates to a method for providing treatment to the human or animal body. Under Rule 67.1(iv), the International Preliminary Examination Authority does not have to carry out an examination on this subject matter.

☐ thedescription, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 11

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furniahed or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International aplication No.
PCT/KR00/01047

V. Reasoned statement under Article 35(2) with regard to n velty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1 - 10, 12 - 13	YES
	Claims		NO
Inventive step (IS)	Claims	1 - 10, 12 - 13	YES
	Claims		NO
Industrial applicability (IA)	Claims	1 - 10, 12 - 13	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Claims 1-10 and 12-13 meet the criteria set forth under PCT Article 33(2), (3) and (4). The use of the claimed isoxazoline derivative in inhibiting the activity of caspases are not anticipated by any of the references on record, and the invention described in the application appears to be new, to involve an inventive step and has industrial application.

PC00010-LG

PCT REQUEST

Original (for **SUBMISSION**) - printed on 18.09.2000 02:49:58 PM

0 0-1	**For receiving Office use only** International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4 0-4-1	**Form - PCT/RO/101 PCT Request** Prepared using	PCT-EASY Version 2.91 (updated 01.07.2000)
0-5	**Petition** The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	Korean Industrial Property Office (RO/KR)
0-7	**Applicant's or agent's file reference**	PC00010-LG
I	**Title of invention**	CASPASE INHIBITOR
II II-1 II-2 II-4 II-5 II-6 II-7 II-8 II-9	**Applicant** This person is: Applicant for Name Address: State of nationality State of residence Telephone No. Facsimile No.	 applicant only all designated States except US LG CHEMICAL LTD. 20, Yoido-dong, Yongdungpo-ku, 150-010 Seoul Republic of Korea KR KR (82-042) 866-2075 (82-042) 863-2053
III-1 III-1-1 III-1-2 III-1-4 III-1-5 III-1-6 III-1-7	**Applicant and/or inventor** This person is: Applicant for Name (LAST, First) Address: State of nationality State of residence	 applicant and inventor US only KIM, Eunice, Eun-Kyeong LG Apt. 8-506, 381-42, Doryong-dong, Yuseong-ku, 305-340 Daejeon Republic of Korea KR KR

PCT REQUEST

PC00010-LG

Original (for **SUBMISSION**) - printed on 18.09.2000 02:49:58 PM

III-2	**Applicant and/or inventor**	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	PARK, Mi-Jeong
III-2-5	Address:	Expo Apt. 305-402, Jeonmin-dong, Yuseong-ku, 305-390 Daejeon Republic of Korea
III-2-6	State of nationality	KR
III-2-7	State of residence	KR
III-3	**Applicant and/or inventor**	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	LEE, Tae-Hee
III-3-5	Address:	LG Apt. 7-505, 381-42, Doryong-dong, Yuseong-ku, 305-340 Daejeon Republic of Korea
III-3-6	State of nationality	KR
III-3-7	State of residence	KR
III-4	**Applicant and/or inventor**	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	CHANG, Hye-Kyung
III-4-5	Address:	LG Apt. 8-204, 381-42, Doryong-dong, Yuseong-ku, 305-340 Daejeon Republic of Korea
III-4-6	State of nationality	KR
III-4-7	State of residence	KR
III-5	**Applicant and/or inventor**	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	PARK, Tae-Kyo
III-5-5	Address:	LG Apt. 8-302, 381-42, Doryong-dong, Yuseong-ku, 305-340 Daejeon Republic of Korea
III-5-6	State of nationality	KR
III-5-7	State of residence	KR

PCT REQUEST

Original (for **SUBMISSION**) - printed on 18.09.2000 02:49:58 PM

III-6	**Applicant and/or inventor**	
III-6-1	This person is:	applicant and inventor
III-6-2	Applicant for	US only
III-6-4	Name (LAST, First)	KANG, Chang-Yuil
III-6-5	Address:	College of Pharmacy, Seoul National University, Shillim-dong, Kwanak-ku, 151-742 Seoul Republic of Korea
III-6-6	State of nationality	KR
III-6-7	State of residence	KR
III-7	**Applicant and/or inventor**	
III-7-1	This person is:	applicant and inventor
III-7-2	Applicant for	US only
III-7-4	Name (LAST, First)	KIM, Young-Myeong
III-7-5	Address:	Department of Molecular and Cellular Biochemistry, Kangwon National University, Kangwon-do, 200-701 Chunchon Republic of Korea
III-7-6	State of nationality	KR
III-7-7	State of residence	KR
III-8	**Applicant and/or inventor**	
III-8-1	This person is:	applicant and inventor
III-8-2	Applicant for	US only
III-8-4	Name (LAST, First)	MOON, Kwang-Yul
III-8-5	Address:	Sammeri Apt. 102-304, Doonsan-dong, Seo-ku, 302-780 Daejeon Republic of Korea
III-8-6	State of nationality	KR
III-8-7	State of residence	KR
III-9	**Applicant and/or inventor**	
III-9-1	This person is:	applicant and inventor
III-9-2	Applicant for	US only
III-9-4	Name (LAST, First)	OH, Young-Leem
III-9-5	Address:	Hyundai Apt. 104-802, Sunhwa-dong, Joong-ku, 301-050 Daejeon Republic of Korea
III-9-6	State of nationality	KR
III-9-7	State of residence	KR

PCT REQUEST

Original (for **SUBMISSION**) - printed on 18.09.2000 02:49:58 PM

III-10	**Applicant and/or inventor**	
III-10-1	This person is:	applicant and inventor
III-10-2	Applicant for	US only
III-10-4	Name (LAST, First)	MIN, Chang-Hee
III-10-5	Address:	Doongji Apt. 109-1404, Doonsan-dong, Seo-ku, 302-120 Daejeon Republic of Korea
III-10-6	State of nationality	KR
III-10-7	State of residence	KR
III-11	**Applicant and/or inventor**	
III-11-1	This person is:	applicant and inventor
III-11-2	Applicant for	US only
III-11-4	Name (LAST, First)	CHUNG, Hyun-Ho
III-11-5	Address:	LG Apt. 9-205, 381-42, Doryong-dong, Yuseong-ku, 305-340 Daejeon Republic of Korea
III-11-6	State of nationality	KR
III-11-7	State of residence	KR
IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	CHOI, Kyu-Pal
IV-1-2	Address:	824-11, Yeoksam-dong, Kangnam-ku, 135-080 Seoul Republic of Korea
IV-1-3	Telephone No.	(82-2) 555-6888
IV-1-4	Facsimile No.	(82-2) 555-9888
IV-1-5	e-mail	HANSUNGP@chollian.net

PCT REQUEST

PC00010-LG

Original (for **SUBMISSION**) - printed on 18.09.2000 02:49:58 PM

V	**Designation of States**	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
V-5	**Precautionary Designation Statement** In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	**Exclusion(s) from precautionary designations**	NONE
VI-1	**Priority claim of earlier international application**	
VI-1-1	Filing date	17 September 1999 (17.09.1999)
VI-1-2	Number	PCT/KR99/00561
VI-1-3	PCT receiving Office	KR
VI-2	**Priority claim of earlier national application**	
VI-2-1	Filing date	04 November 1999 (04.11.1999)
VI-2-2	Number	1999-48608
VI-2-3	Country	KR

PC00010-LG

PCT REQUEST

Original (for **SUBMISSION**) - printed on 18.09.2000 02:49:58 PM

VII-1	**International Searching Authority Chosen**	Korean Industrial Property Office (KIPO) (ISA/KR)	
VIII	**Check list**	number of sheets	electronic file(s) attached
VIII-1	Request	6	-
VIII-2	Description	133	-
VIII-3	Claims	14	-
VIII-4	Abstract	1	00010.txt
VIII-5	Drawings	16	-
VIII-7	TOTAL	170	
	Accompanying items	paper document(s) attached	electronic file(s) attached
VIII-8	Fee calculation sheet	✓	-
VIII-9	Separate signed power of attorney	✓	-
VIII-12	Priority document(s)	Item(s) VI-1, VI-2	-
VIII-16	PCT-EASY diskette	-	diskette
VIII-18	**Figure of the drawings which should accompany the abstract**	1	
VIII-19	**Language of filing of the international application**	English	
IX-1	**Signature of applicant or agent**		
IX-1-1	Name (LAST, First)	CHOI, Kyu-Pal	

FOR RECEIVING OFFICE USE ONLY

10-1	**Date of actual receipt of the purported international application**	
10-2	**Drawings:**	
10-2-1	Received	
10-2-2	Not received	
10-3	**Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application**	
10-4	**Date of timely receipt of the required corrections under PCT Article 11(2)**	
10-5	**International Searching Authority**	ISA/KR
10-6	**Transmittal of search copy delayed until search fee is paid**	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	**Date of receipt of the record copy by the International Bureau**	

PCT (ANNEX - FEE CALCULATION SHEET)

PC00010-LG

Original (for SUBMISSION) - printed on 18.09.2000 02:49:58 PM

(This sheet is not part of and does not count as a sheet of the international application)

0 0-1	**For receiving Office use only** International Application No.				
0-2	Date stamp of the receiving Office				
0-4 0-4-1	**Form - PCT/RO/101 (Annex)** **PCT Fee Calculation Sheet** Prepared using	PCT-EASY Version 2.91 (updated 01.07.2000)			
0-9	**Applicant's or agent's file reference**	PC00010-LG			
2	**Applicant**	LG CHEMICAL LTD., et al.			
12	**Calculation of prescribed fees**	fee amount/multiplier		total amounts (KRW)	
12-1	Transmittal fee T	⇨		45,000	
12-2	Search fee S	⇨		150,000	
12-3	International fee Basic fee (first 30 sheets) b1	426,800			
12-4	Remaining sheets	140			
12-5	Additional amount (X)	9,800			
12-6	Total additional amount b2	1,372,000			
12-7	b1 + b2 = B	1,798,800			
12-8	Designation fees Number of designations contained in international application	87			
12-9	Number of designation fees payable (maximum 8)	8			
12-10	Amount of designation fee (X)	91,900			
12-11	Total designation fees D	735,200			
12-12	PCT-EASY fee reduction R	-131,300			
12-13	Total International fee (B+D-R) I	⇨		2,402,700	
12-17	**TOTAL FEES PAYABLE (T+S+I+P)**	⇨		2,597,700	
12-19	**Mode of payment**	cash			

VALIDATION LOG AND REMARKS

13-2-4	**Validation messages** **Priority**	Yellow! Priority 1: The twelve-month time limit for claiming priority would appear to have expired. Please verify.
13-2-10	**Validation messages** **For receiving Office/International Bureau use only**	Green? Verify electronic data for consistency against printed form.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR00/01047

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 261/04, A61K 31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimun documentation searched (classification system followed by classification symbols)
IPC7 C07D, A61K

Documentation searched other than minimun documentation to the extent that such documents are included in the fileds searched
Korean patents and applications for inventions since 1975

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search trerms used)
CA(STN), Medline

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5686434 A(Pfizer Inc.) 11. 11.1997 abstract, claims	6-12
A	US 5716967 A(Pfizer Inc.) 02. 10 .1998 abstract, claims	6-12
A	JP 11-180891 A(Daiichi Seiyaku. Co. LTD.) 06.07.1999 abstract, claims	6
A	EP 749428 A(Pfizer Inc.) 27. 12 .1996 abstract	6-12
A	J. Y. Lee 'synthesis of hexapeptide and tetrapeptide analogs of the immunomodulating peptides' J.Chem. Soc., Perkin Trans. , 1998, Vol.1, No.2, 359-366	1-5, 13
X, P	KR 1999-79268 A(LG Chem.LTD.)05.11.1999 see the whole document	1-13

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevence
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevence; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevence; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 DECEMBER 2000 (29.12.2000)	29 DECEMBER 2000 (29.12.2000)

Name and mailing address of the ISA/KR	Authorized officer
Korean Industrial Property Office Government Complex-Taejon, Dunsan-dong, So-ku, Taejon Metropolitan City 302-701, Republic of Korea Facsimile No. 82-42-472-7140	LEE, Tae Young Telephone No. 82-42-481-5607

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR00/01047

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11
because they relate to subject matter not required to be searched by this Authority, namely:
although claim 11 is directed to a method of treatment of human body, the search has been carried out and based on the alleged effects of the compound or composition.

2. [ ] Claims Nos.:
because they relate to part of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Search Authority found multiple inventions in this international application, as follows:

1. [ ] As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be established without effort justifying an additional fee, this Authority did not invite payment of any addition fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR00/01047

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5686434 A	11.11.1997	WO 95/14680 A	01.06.1995
		EP 730587 A	11.09.1996
		JP 09-500146 T	07.01.1997
US 5716967 A	11.11.1997	WO 95/14681 A	01.06.1995
		EP 730588 A	11.09.1996
		JP 09-500147 T	07.01.1997
EP 749428 A	27.12.1996	WO 95/24398 A	14.09.1995
		US 5869511 A	09.02.1999
		JP 09-505082 T	20.05.1997

ATENT COOPERATION TRE

From the RECEIVING OFFICE

To:

CHOI, Kyu Pal

824-11, Yeoksam-dong, Kangnam-ku, Seoul 135-080,
Republic of Korea

PCT

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rule 59.3(e) and 61.1(b), first sentence and Administrative Instructions, Section 601(a))

Date of mailing *(day/month/year)* 14 FEBRUARY 2001 (14.02.2001)

Applicant's or agent's file reference
PC00010-LG

IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/KR00/01047	18 SEPTEMBER 2000 (18.09.2000)	17 SEPTEMBER 1999 (17.09.1999)

Applicant

LG CHEMICAL LTD. et al

1. The applicant is hereby **notified** that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

05 FEBRUARY 2001 (05.02.2001)

2. This date of receipt is :

[X] the actual date of receipt of the demand by this Authority (Rule 61.1(b)).

[ ] the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).

[ ] the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. [ ] **ATTENTION**: That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

[ ] *(If applicable)* This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/KR	Authorized officer
Korean Industrial Property Office Government Complex-Taejon, Dunsan-dong, So-ku, Taejon Metropolitan City 302-701, Republic of Korea	COMMISSIONER
Facsimile No. 82-42-472-7140	Telephone No. 82-42-481-5210

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ KR

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: PC0[illegible]010-LG

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/KR00/01047	18 September 2000(18.09.00)	17 September 1999(17.09.99)

Title of invention

CASPASE INHIBITOR

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

LG CHEMICAL LTD.
20, Yoido-dong, Yongdungpo-ku,
Seoul 150-010, Republic of Korea

Telephone No.: (82-042) 866-2075

Facsimile No.: (82-042) 863-2053

Teleprinter No.:

State *(that is, country)* of nationality: KR

State *(that is, country)* of residence: KR

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

KIM, Eunice, Eun-Kyeong
LG Apt. 8-506, 381-42, Doryong-dong,
Yuseong-ku, Daejeon 305-340,
Republic of Korea

State *(that is, country)* of nationality: KR

State *(that is, country)* of residence: KR

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

PARK, Mi-Jeong
Expo Apt. 305-402, Jeonmin-dong,
Yuseong-ku, Daejeon 305-390,
Republic of Korea

State *(that is, country)* of nationality KR

State *(that is, country)* of residence KR

[X] Further applicants are indicated on a continuation sheet.

International application No.
PCT/KR00/01047

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

LEE, Tae-Hee
LG Apt. 7-505, 381-42, Doryong-dong,
Yuseong-ku, Daejeon 305-340,
Republic of Korea

State *(that is, country)* of nationality: KR

State *(that is, country)* of residence: KR

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

CHANG, Hye-Kyung
LG Apt. 8-204, 381-42, Doryong-dong,
Yuseong-ku, Daejeon 305-340,
Republic of Korea

State *(that is, country)* of nationality: KR

State *(that is, country)* of residence: KR

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

PARK, Tae-Kyo
LG Apt. 8-302, 381-42, Doryong-dong,
Yuseong-ku, Daejeon 305-340,
Republic of Korea

State *(that is, country)* of nationality: KR

State *(that is, country)* of residence: KR

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

KANG, Chang-Yuil
College of Pharmacy, Seoul National University,
Shillim-dong, Kwanak-ku, Seoul 151-742,
Republic of Korea

State *(that is, country)* of nationality: KR

State *(that is, country)* of residence KR

[X] Further applicants are indicated on another continuation sheet.

International application No.
PCT/KR00/01047

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

KIM, Young-Myeong
Department of Molecular and Cellular Biochemistry,
Kangwon National University,
Chunchon, Kangwon-do 200-701,
Republic of Korea

State *(that is, country)* of nationality: KR

State *(that is, country)* of residence: KR

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

MOON, Kwang-Yul
Sammeri Apt. 102-304, Doonsan-dong,
Seo-ku, Daejeon 302-780,
Republic of Korea

State *(that is, country)* of nationality: KR

State *(that is, country)* of residence: KR

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

OH, Young-Leem
Hyundai Apt. 104-802, Sunhwa-dong,
Joong-ku, Daejeon 301-050,
Republic of Korea

State *(that is, country)* of nationality: KR

State *(that is, country)* of residence: KR

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

MIN, Chang-Hee
Doongji Apt. 109-1404, Doonsan-dong,
Seo-ku, Daejeon 302-120,
Republic of Korea

State *(that is, country)* of nationality KR

State *(that is, country)* of residence KR

[X] Further applicants are indicated on another continuation sheet.

International application No.
PCT/KR00/01047

Continuation f Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

CHUNG, Hyun-Ho
LG Apt. 9-205, 381-42, Doryong-dong,
Yuseong-ku, Daejeon 305-340,
Republic of Korea

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
KR	KR

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality	State *(that is, country)* of residence

☐ Further applicants are indicated on another continuation sheet.

International application No.
PCT/KR00/01047

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [X] agent [ ] common representative

and [X] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

CHOI, Kyu-Pal
824-11, Yeoksam-dong, Kangnam-ku,
Seoul 135-080, Republic of Korea

Telephone No.: (82-2) 555-6888

Facsimile No.: (82-2) 555-9888

Teleprinter No.:

[ ] **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special addr ess to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination **to start on the basis of:**

[X] the international application as originally filed

the description [ ] as originally filed
[ ] as amended under Article 34

the claims [ ] as originally filed
[ ] as amended under Article 19 (together with any accompanying statement)
[ ] as amended under Article 34

the drawings [ ] as originally filed
[ ] as amended under Article 34

2. [ ] The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. [ ] The applicant wishes the start of the international preliminary examination **to be postponed** until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

[X] which is the language in which the international application was filed.
[ ] which is the language of a translation furnished for the purposes of international search.
[ ] which is the language of publication of the international application.
[ ] which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby **elects all eligible States** *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes **not to elect:**

International application No.
PCT/KR00/01047

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. [X] fee calculation sheet
2. [ ] separate signed power of attorney
3. [ ] copy of general power of attorney; reference number, if any:
4. [ ] statement explaining lack of signature
5. [ ] nucleotide and or amino acid sequence listing in computer readable form
6. [ ] other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

CHOI, Kyu-Pal

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. [ ] The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. [ ] The applicant has been informed accordingly.
4. [ ] The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. [ ] Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

See Notes to the demand form

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

International application No.	PCT/KR00/01047
Applicant's or agent's file reference	PC00010-LG
Applicant	LG CHEMICAL LTD. et al.

For International Preliminary Examining Authority use only

Date stamp of the IPEA

Calculation of prescribed fees

1. Preliminary examination fee	150,000 P	
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	152,600 H	
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	302,600 TOTAL	

Mode of Payment

☐	authorization to charge deposit account with the IPEA (see below)	☒	cash
☐	cheque	☐	revenue stamps
☐	postal money order	☐	coupons
☐	bank draft	☐	other *(specify)*:

Deposit Account Authorization *(this mode of payment may not be available at all IPEAs)*

The IPEA/ _____ ☐ is hereby authorized to charge the total fees indicated above to my deposit account.

☐ *(this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

Deposit Account Number	Date *(day/month/year)*	Signature

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

To:

CHOI, Kyu-Pal
824-11, Yeoksam-dong
Kangnam-ku
Seoul 135-080
RÉPUBLIQUE DE CORÉE

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

Date of mailing (day/month/year) 20 September 2001 (20.09.01)	
Applicant's or agent's file reference PC00010-LG	**IMPORTANT NOTIFICATION**
International application No. PCT/KR00/01047	**International filing date** (day/month/year) 18 September 2000 (18.09.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
LG CHEMICAL LTD. 20, Yoido-dong Yongdungpo-ku Seoul 150-010 Republic of Korea	KR	KR
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
LG CHEM INVESTMENT LTD. 20, Yoido-dong Yongdungpo-ku Seoul 150-010 Republic of Korea	KR	KR
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Idhir BRITEL
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994) 004304237

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
CHOI, Kyu Pal

824-11, Yeoksam-dong, Kangnam-ku, Seoul 135-080, Republic of Korea

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)* 15 JANUARY 2002 (15.01.2002)	
Applicant's or agent's file reference PC00010-LG	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/months/year)*
PCT/KR00/01047	18 SEPTEMBER 2000 (18.09.2000)	17 SEPTEMBER 1999 (17.09.1999)

Applicant

LG CHEMICAL LTD. et al

1. The applicant is hereby notified that International Preliminary Examining Authority transmits here with the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report(but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details in the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/KR Korean Intellectual Property Office Government Complex-Daejeon, Dunsan-dong, Seo-gu, Daejeon Metropolitan City 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer COMMISSIONER Telephone No. 82-42-481-5210

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Artcle 36 and Rule 70)

Applicant's or agent's file reference PC00010-LG	**FOR FURTHER ACTION**	SeeNotificationofTransmittalofInternationalPreliminary Examination Report (Form PCT/IPEA/416)
International application No. **PCT/KR00/01047**	International filing date*(day/month/year)* 18 SEPTEMBER 2000 (18.09.2000)	Priority date *(day/month/year)* 17 SEPTEMBER 1999 (17.09.1999)
International Patent Classification (IPC) or national classification and IPC **IPC7 C07D 261/04, A61K 31/41**		
Applicant LG CHEMICAL LTD. et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demamd 05 FEBRUARY 2001 (05.02.2001)	Date of completion of this report 10 JANUARY 2002 (10.01.2002)
Name and mailing address of the IPEA/KR Korean Intellectual Property Office Government Complex-Daejeon, Dunsan-dong, Seo-gu, Daejeon Metropolitan City 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer CHO, Hee Won Telephone No. 82-42-481-5607

Form PCT/IPEA/409 (cover sheet) (July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International aplication No.
PCT/KR00/01047

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed

☐ the description:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☐ the claims:
pages _____ , as originally filed
pages _____ , as amended (together with any statment) under Article 19
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☐ the drawings:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☐ the sequence listing part of the description:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application(under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide** and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained inthe international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disc losure in the international applicationas as filed has been furinshed.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheet _____

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box(Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed." and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International aplication No.
PCT/KR00/01047

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☐ claims Nos. _____

because:

☒ the said international application, or the said claims Nos. 11
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

Claim 11 relates to a method for providing treatment to the human or animal body. Under Rule 67.1(iv), the International Preliminary Examination Authority does not have to carry out an examination on this subject matter.

☐ thedescription, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 11

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furniahed or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International aplication No.
PCT/KR00/01047

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1 - 10, 12 - 13	YES
	Claims		NO
Inventive step (IS)	Claims	1 - 10, 12 - 13	YES
	Claims		NO
Industrial applicability (IA)	Claims	1 - 10, 12 - 13	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Claims 1-10 and 12-13 meet the criteria set forth under PCT Article 33(2), (3) and (4). The use of the claimed isoxazoline derivative in inhibiting the activity of caspases are not anticipated by any of the references on record, and the invention described in the application appears to be new, to involve an inventive step and has industrial application.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

CHOI, Kyu Pal

824-11, Yeoksam-dong, Kangnam-ku, Seoul 135-080, Republic of Korea

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 30 DECEMBER 2000 (30.12.2000)
Applicant's or agent's file reference PC00010-LG	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. **PCT/KR00/01047**	Intrenational filing date *(day/month/year)* 18 SEPTEMBER 2000 (18.09.2000)
Applicant LG CHEMICAL LTD. et al	

1. [X] The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsilime No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
[ ] the protest together with the decision theron has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision theron to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, nust reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively. before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/KR Korean Industrial Property Office Government Complex-Taejon, Dunsan-dong, So-ku, Taejon Metropolitan City 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer COMMISSIONER Telephone No. 82-42-481-5131

Form PCT/ISA/220 (July 1998)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PC00010-LG	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. **PCT/KR00/01047**	International filing date *(day/month/year)* 18 SEPTEMBER 2000 (18.09.2000)	(Earliest) Priority Date *(day/month/year)* 17 SEPTEMBER 1999 (17.09.1999)
Applicant LG CHEMICAL LTD. et al		

This International search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:
      ☐ contained in the international application in written form.
      ☐ filed together with the international application in computer readable form.
      ☐ furnished subsequently to this Authority in written form.
      ☐ furnished subsequently to this Authority in computer readable form.
      ☐ the statement that the subsequenlty furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
      ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (See Box II).

4. With regard to the **title**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawing** to be published with the abstract is Figure No. 1
   ☒ as suggested by the applicant. ☐ None of the figures.
   ☐ because the applicant failed to suggest a figure.
   ☐ because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR00/01047

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11
because they relate to subject matter not required to be searched by this Authority, namely:
although claim 11 is directed to a method of treatment of human body, the search has been carried out and based on the alleged effects of the compound or composition.

2. [ ] Claims Nos.:
because they relate to part of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Search Authority found multiple inventions in this international application, as follows:

1. [ ] As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be established without effort justifying an additional fee, this Authority did not invite payment of any addition fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR00/01047

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 261/04, A61K 31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimun documentation searched (classification system followed by classification symbols)

IPC7 C07D, A61K

Documentation searched other than minimun documentation to the extent that such documents are included in the fileds searched

Korean patents and applications for inventions since 1975

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search trerms used)

CA(STN), Medline

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5686434 A(Pfizer Inc.) 11. 11.1997 abstract, claims	6-12
A	US 5716967 A(Pfizer Inc.) 02. 10 .1998 abstract, claims	6-12
A	JP 11-180891 A(Daiichi Seiyaku. Co. LTD.) 06.07.1999 abstract, claims	6
A	EP 749428 A(Pfizer Inc.) 27. 12 .1996 abstract	6-12
A	J. Y. Lee 'synthesis of hexapeptide and tetrapeptide analogs of the immunomodulating peptides' J.Chem. Soc., Perkin Trans. , 1998, Vol.1, No.2, 359-366	1-5, 13
X, P	KR 1999-79268 A(LG Chem.LTD.)05.11.1999 see the whole document	1-13

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevence

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevence; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevence; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 DECEMBER 2000 (29.12.2000)	29 DECEMBER 2000 (29.12.2000)

Name and mailing address of the ISA/KR	Authorized officer
Korean Industrial Property Office Government Complex-Taejon, Dunsan-dong, So-ku, Taejon Metropolitan City 302-701, Republic of Korea	LEE, Tae Young
Facsimile No. 82-42-472-7140	Telephone No. 82-42-481-5607

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR00/01047

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5686434 A	11.11.1997	WO 95/14680 A	01.06.1995
		EP 730587 A	11.09.1996
		JP 09-500146 T	07.01.1997
US 5716967 A	11.11.1997	WO 95/14681 A	01.06.1995
		EP 730588 A	11.09.1996
		JP 09-500147 T	07.01.1997
EP 749428 A	27.12.1996	WO 95/24398 A	14.09.1995
		US 5869511 A	09.02.1999
		JP 09-505082 T	20.05.1997

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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29 March 2001 (29.03.2001)

PCT

(10) International Publication Number
WO 01/21600 A1

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(21) International Application Number: PCT/KR00/01047

(22) International Filing Date:
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(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/KR99/00561
17 September 1999 (17.09.1999) KR
1999/48608 4 November 1999 (04.11.1999) KR

(71) Applicant *(for all designated States except US)*: **LG CHEMICAL LTD.** [KR/KR]; 20, Yoido-dong, Yongdungpo-ku, Seoul 150-010 (KR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KIM, Eunice, Eun-Kyeong** [KR/KR]; LG Apt. 8-506, 381-42, Doryong-dong, Yuseong-ku, Daejeon 305-340 (KR). **PARK, Mi-Jeong** [KR/KR]; Expo Apt., 305-402, Jeonmin-dong, Yuseong-ku, Daejeon 305-390 (KR). **LEE, Tae-Hee** [KR/KR]; LG Apt. 7-505, 381-42, Doryong-dong, Yuseong-ku, Daejeon 305-340 (KR). **CHANG, Hye-Kyung** [KR/KR]; LG Apt. 8-204, 381-42, Doryong-dong, Yuseong-ku, Daejeon 305-340 (KR). **PARK, Tae-Kyo** [KR/KR]; LG Apt. 8-302, 381-42, Doryong-dong, Yuseong-ku, Daejeon 305-340 (KR). **KANG, Chang-Yuil** [KR/KR]; College of Pharmacy, Seoul National University, Shillim-dong, Kwanak-ku, Seoul 151-742 (KR). **KIM, Young-Myeong** [KR/KR]; Dept. of Molecular and Cellular Biochemistry, Kangwon National University, Kangwon-do, Chunchon 200-701 (KR). **MOON, Kwang-Yul** [KR/KR]; Sammeri Apt., 102-304, Doonsan-dong, Seo-ku, Daejeon 302-780 (KR). **OH, Young-Leem** [KR/KR]; Hyundai Apt., 104-802, Sunhwa-dong, Joong-ku, Daejeon 301-050 (KR). **MIN, Chang-Hee** [KR/KR]; Doongji Apt., 109-1404, Doonsan-dong, Seo-ku, Daejeon 302-120 (KR). **CHUNG, Hyun-Ho** [KR/KR]; LG Apt. 9-205, 381-42, Doryong-dong, Yuseong-ku, Daejeon 305-340 (KR).

(74) Agent: **CHOI, Kyu-Pal**; 824-11, Yeoksam-dong, Kangnam-ku, Seoul 135-080 (KR).

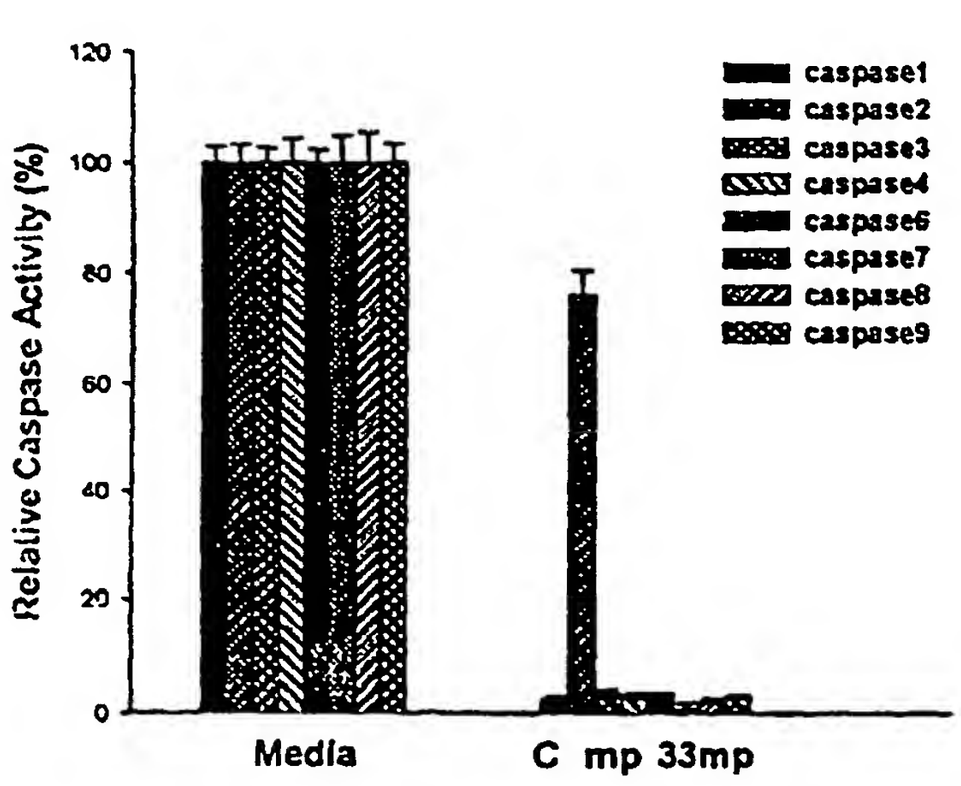
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: CASPASE INHIBITOR

(57) Abstract: The present invention relates to an isoxazoline derivative of formula (I), the pharmaceutically acceptable salts, esters and stereochemically isomeric forms thereof, and the use of the derivative in inhibiting the activity of caspases. The present invention also relates to a pharmaceutical composition for preventing inflammation and apotosis which comprises the isoxazoline derivative, pharmaceutically acceptable salts, esters and stereochemically isomeric forms thereof and the process for preparing the same. The derivative according to the present invention can be effectively used in treating diseases due to caspases, such as, for example the disease in which cells are abnormally died, dementia, cerebral stroke, AIDS, diabetes, gastric ulcer, hepatic injure by hepatitis, sepsis, organ transplantation rejection reaction and anti-inflammation.



WO 01/21600 A1

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

10/PRTS

CASPASE INHIBITOR

Technical Field

The present invention relates to a novel isoxazoline derivative, pharmaceutically acceptable salts, esters and stereochemically isomeric forms thereof which can serve as an inhibitor for protein caspases (cysteinyl-aspartate proteinases), a process for preparing the same and the use of the derivative as an inhibitor for caspases. The present invention also relates to a pharmaceutical composition for preventing inflammation and apoptosis which comprises the isoxazoline derivative, pharmaceutically acceptable salts, esters and stereochemically isomeric forms thereof and the process for preparing the same. The isoxazoline derivative according to the present invention can effectively be used in treating diseases due to caspases, for example, the disease in which cells are abnormally died, dementia, cerebral stroke, AIDS, diabetes, gastric ulcer, hepatic injure by hepatitis, sepsis, organ transplantation rejection reaction and anti-inflammation.

Background Art

All organisms in nature undergo the life cycle consisting of development, differentiation, growth and death. Recently, an extensive research has been made to a mechanism involved in apoptosis which would play a key role in the control of the life cycle and the outbreak of diseases. It has been reported that apoptosis is occurred by a number of factors, but largely due to three kinds of cellular signal transport systems: the first of which is a signal transport system by the protein-protein interaction (See, Muzio M. et al., *Cell* 85, 817, 1996; Humke E. W. et al., *JBC* 273, 15702, 1998), the

second, an incorporation of cytochrome C into cytoplasm via mitochondria (See, Liu X. et al., *Cell* 86:147, 1996; Li P. et al., *Cell* 91, 479, 1997), and the third, a cellular signal transport pathway by the SAPK(Stress-activated protein kinases) activation of mitogen-activation protein kinase(MAPK) enzymes. All the pathways have been known to activate caspases cascade. As such caspases, about 10 kinds of isoenzymes in human and 14 kinds in mouse have been identified (see, Thornberry N. A. et al., *Science* 28, 1312 1998; Green D. R. *Science* 28, 1309, 1998; Ahmad M., et al., *Cancer Res.* 15, 5201 1998). The enzymes exist within the cells in the form of proenzyme which has no enzymatic activity and converted into an activated form if the cells are damaged or are exposed to a substance which leads to cellular necrosis. An activated enzyme has a heterodimer structure in which two polypeptides, i.e. larger subunits with the molecular weight of about 17-20 kDa, and smaller subunits with the molecular weight of about 10 kDa are bound together.

At present, caspases are classified into three (3) groups in view of the genetic identification analysis results and the biochemical characteristics: the first group is caspase-1, 4 and 5 which are responsible for the processing of cytokine activation, the second is caspase-3, 6 and 7 which carry out apoptosis and the third is caspase-8, 9 and 10 which are responsible for enzymatic activation in the upstream of signal transport system of apoptosis.

Among these caspases, Caspase-3 group and Caspase-8, 9, 10 etc. were recently reported to be related to apoptosis, and diseases (see, Thornberry N.A. et al., *Science*, 28, 1312, 1998).

According to the recent research results, caspases are commonly activated as apoptosis is initiated, even though there is a minor difference depending upon the tissues and cells. The activated caspases then activate intracellular CAD(Caspase-activated DNAse) which finally digests intranuclear DNA to result in cell death (Sakahira H., et al., *Nature* 1 96, 1998; Enari M et al., *Nature* 1 43, 1998). In addition, they promote apoptosis by decomposing substrate such as PARP (Poly-ADP ribose polymerase) which is necessary for the survival of cells.

Meantime, according to the recent disease-related researches, it was reported that the activity of Caspase-3 is increased in the brain of dementia patient which promotes the production of beta-amyloid peptide from beta-amyloid precursor protein that is considered to be a major cause of dementia, thereby accelerating the apoptosis of brain cells (see, Kuida K. et al., *Nature* 28, 368, 1996). Further, it was reported that activation of caspases can be the direct inducer of various diseases such as sepsis (see, Haendeler J. et al., *Shock* 6, 405, 1996; Lenhoff R.J. et al., 29, 563, 1999), rheumatoid arthritis (Firestein G.S. et al., *J. Clin. Invest* 96(3), 1631, 1995), cerebral stroke (see, Hill I.E. et al., *Brain Res.*10, 398, 1995), ALS disease (see, Alexianu M.E. et al., *J. Neurochem* 63, 2365, 1994), autoimmune isease (see, Rieux-Laucat F, et al., *Science* 2, 1347, (1995), diabetes mellitusd(see, Juntti-Berggren et al., *Science* 2, 86, 1993), hepatitis (Haendeler J. et al., *Shock* 6, 405, 1996), organ transplantation rejection reaction (Koglin J. et al., *Transplantation*, 27, 904, 1999; Bergese S.D. et al., *Transplantation* 27, 904, 1999), gastric ulcer (see, Slomiany B.L. et al., *J. Physiol. Pharmacol.* 96, 1631, 1995), and the like.

The researches on three dimensional structure of caspase-1 and caspase-3, catalytic mechanism of the enzyme and enzyme-substrate specificity (see,

Wilson, K.P et al., *Nature* 370, 270, 1994; Walker, N.P.C. et al., *Cell* 78, 343, 1994; *Nature Struc. Biol.* 3, 619, 1996) revealed that Caspase-1 group has a hydrolase-substrate specificity for the peptide sequence of (P4)-Val-X-Asp(P1) and Caspase-3 group has a hydrolase-substrate specificity for the sequence of (P4)Asp-X-X-Asp(P1).

Z-VAD-fluoromethyl ketone, and Z-DEVD-fluoromethyl ketone which mimics the above amino acid sequence have already been used in the researches on the inhibitors and were proven to have an inhibitory activity on apoptosis of hepatic cells by an activation of caspases (see, Rodriguez I. Et al., *J. Exp. Med.*, 184, 2067, 1996; Rouquet N. et al., *Curr Biol.* 1, 1192, 1996; Kunstle G. et al., *Immunol. Lett* 55, 5, 1997), and on the apoptosis of brain cells by cerebral ischemias. However, since such peptide derivatives are deficient in drug property for clinical application, they cannot be used as therapeutics.

Fulminant hepatic failure (FHF) is a clinical syndrome resulting from massive death of liver cells or sudden and severe impairment of liver function (See: Trey, C. et al., 1970, *Progress in liver disease*, Popper, H. and F. Schaffner, eds. Grune and stratton, New York, pp282-298). The causes of FHF are diverse: hepatitis virus infection, drugs and toxins, alcohol, ischemia, metabolic disorder, massive malignant infiltration, chronic autoimmune hepatitis, etc. However, these mechanisms are not completely clear. Since the prognosis of FHF is very poor while its progress is very rapid, it is not uncommon that a patient falls in lethal condition in 1-2 weeks from the onset of this syndrome (See, Sherlock, S. 1993, *Adv. Intern. Med.* 38: 245-267). Consequently, the overall mortality in most series is very high. However, the hepatic lesion is potentially reversible, and survivors usually recover completely.

Different therapeutic options that have been tried in FHF include antibiotics, diuretics, corticosteroids, blood transfusion, charcoal haemoperfusion, and plasmaphresis. However, none of these methods have been shown to be effective in controlled studies. In recent years, liver transplantation is generally accepted as the only therapeutic option to actually improve the prognosis of this syndrome. However, liver transplantation cannot be the perfect treatment for FHF because of immune complication, viral or bacterial infection, and graft availability. Thus, a potent therapeutic agent which can protect hepatic cells from massive death during the acute phase is critically desired.

Apoptosis is a type of cell death characterized by a series of distinct morphological and biochemical changes accomplished by specialized cellular machinery. Apoptosis is an essential process to remove excess, unwanted and harmful cells and maintain homeostasis, but inappropriate apoptosis is implicated in many human diseases such as neurodegenerative diseases, ischaemic damage, autoimmune disorders, several forms of cancer. Recently, it became clear that apoptosis of hepatocytes is a critical cause of hepatic injury in viral hepatitis and alcoholic hepatitis and acute hepatic failure in fulminant hepatitis. Many changes which occur in a cell that received apoptotic signal reflect complex biochemical events carried out by a family of cysteine proteases called caspases.

Caspases inactivate proteins that protect living cells from apoptosis, such as I^{CAD}/DFF45, an inhibitor of the nuclease responsible for DNA fragmentation, and Bcl-2. At the same time, caspases contribute to apoptosis not only by direct disassembly of cell structures, but also by reorganizing cell structures indirectly by cleaving several proteins involved

in cytoskeleton regulation. Since caspase activation is closely related to the initiating, propagating, and terminal event of most forms of apoptosis, this family of enzymes are attractive potential targets for the treatment of disorders resulted from excessive apoptosis or insufficient apoptosis.

Several kinds of caspase inhibitors have been identified. Four distinct classes of viral inhibitors have been described: CrmA, p35, a family of IAP (inhibitors of apoptosis), and the hepatitis B virus-encoded HBx protein (See, Gottlob, K. et al., 1998, *J. Biol. Chem.* 273: 33347-33353). However, these molecules are not suitable as the therapeutic agent. Peptide-based caspase inhibitor such as z-VAD-fmk, z-DEVD-fmk, and Ac-YVAD-cmk has widely been used for research use and this inhibitor showed apoptosis-blocking activity in cellular level (See: Sane, A. T. et al., 1998, Cancer Res. 58: 3066-3072), in rodent models of liver injury caused by Fas or by TNF_{α} (See: Kunstle, G. et al., 1997, *Immunol. Lett.* 55: 5-10) or ischemia after liver transplantation (See: Cursio, R. et al., 1999, *FASEB J.* 13: 253-261). Petak and colleagues showed that a bi-functional anticancer agent, BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea) had caspase inhibiting activity and inhibited drug-induced apoptosis *in vitro* (See: Petak, I. et al., 1998, *Cancer Res.* 58: 614-618). Recently, cyclooxygenase-2 (COX-2) inhibitors are arousing interest as potential therapeutic agents of FHF (See, McCormick, P. A. et al., 1999, *Lancet* 353: 40-41). However, the efficacy of these materials has not been clinically verified yet.

In the meantime, development of new drugs depends primarily on the availability of suitable animal models relevant to human hepatitis or hepatocytic damage. It is therefore very important to adopt a suitable animal model relevant to human FHF to test efficacy of a candidate for

therapeutic agent. Two types of experimental hepatitis model were reported. One is hepatic injury induced by bacterial lipopolysaccharide together with D-galactosamine (See: Galanos, C. et al., 1979, *Proc. Natl. Acad. Sci.*, 76: 5939; Lehman, V. et al., 1987, *J. Exp. Med.* 165-657), and the other is a recently developed experimental model, Con A-induced hepatitis (See: Tiegs, G. et al., 1992, *J. Clin. Invest.* 90: 196-203; .Mizuhara, H. et al., 1994, *J. Exp. Med.* 179: 1529-1537). Con A-induced hepatitis model closely mimics human FHF in many respects, especially in the role of Fas in pathogenesis. Fas is abundantly expressed on the hepatocyte and FasL is expressed on activated T cells and functions as an effector of cytotoxic lymphocytes. Injection of agonistic monoclonal anti-Fas antibody into adult mice caused rapid hepatic failure, indicating that abnormally activated Fas-FasL system may play a role in human fulminant hepatitis which can be caused by the activation of immune system such as cytotoxic T cells. Accumulating data such as the involvement of specific CTLs in the pathogenesis of FHF, the sensitivity of primary hepatocytes to Fas-mediated apoptosis *in vitro*, and the overexpression of Fas in hepatocytes transformed with human hepatitis virus are consistent with this hypothesis. In recent studies, the activation of Fas-FasL system has been proved to play an important role in the liver cell injury by Con A-induced hepatitis (See: Tagawa, Y. et al., 1998, *Eur. J. Immunol.* 28: 4105-4113). FasL was induced in the liver shortly after the Con A injection was predominantly expressed on intrahepatic T cells. These results indicate thar Fas-FasL system is a critical element in the development of Con A-induced hepatitis. At the same time, the induction of Con A-hepatitis is associated with the production of various cytokines such as IL-2, TNF_{α} , IL-6, IL-4, and IL-10.

Disclosure of Invention

The present inventors have conducted an extensive research for many years in order to develop new therapeutics suitable for caspase inhibitor which has a unique structure over those known in the art. As a result, the inventors have surprisingly discovered a novel isoxazoline derivative of formula (I) which has a different structure over the known inhibitors and has an excellent inhibitory activity against various substrates for caspases, and have completed the present invention.

It is therefore an object of the present invention to provide a novel isoxazoline compound of the formula (I), the pharmaceutically acceptable salts, esters and stereochemically isomeric forms thereof which are useful as a caspase inhibitor.

Another object of the present invention is to provide a process for preparing the compound of formula (I).

Further object of the present invention is to provide a caspase inhibitor which comprises an isoxazoline derivative of the formula (I), the pharmaceutically acceptable salts, esters and stereochemically isomeric forms thereof.

Still other object of the present invention is to provide a pharmaceutical composition for inhibiting caspases activity which comprises as the active ingredient a therapeutically effective amount of the isoxazoline derivative of formula (I) and pharmaceutically acceptable carrier.

Still further object of the present invention is to provide a pharmaceutical composition for preventing inflammation and apoptosis which comprises the isoxazoline derivative, pharmaceutically acceptable salts, esters and

stereochemically isomeric forms thereof and the process for preparing the same.

Further objects and advantages of the invention will become apparent through reading the remainder of the specification.

The foregoing has outlined some of the more pertinent objects of the present invention. These objects should be construed to be merely illustrative of some of the more pertinent features of the invention. Many other beneficial results can be obtained by applying the disclosed invention in a different manner or by modifying the invention within the scope of the disclosure. Accordingly, other objects and a more thorough understanding of the invention may be found by referring to the detailed description of the preferred embodiment in addition to the scope of the invention defined by the claims.

Brief Description Of Drawings

Fig. 1 represents a graph showing inhibition activity of the compound of the invention against recombinant caspase-1, -2, -3, -4, -6, -7, -8 and -9.

Fig. 2 represents a graph showing caspase inhibition activities of the compound of the invention in rat hepatocytes in which apoptosis was derived by TNF_{α} and Actinomycin D treatment.

Fig. 3 represents a graph showing the effect of the compound of the invention on the prevention of apoptosis in rat hepatocytes in which apoptosis were derived by TNF_{α} and Actinomycin D treatment.

Fig. 4 represents a dose-dependent inhibitory activity of the compound of the invention against AST and ALT activities elevated by ConA *in vivo*, wherein the crossbars show the average of each group and p value was calculated by student's t-test.

Fig. 5 represents a dose-dependent inhibition activity against cytokines elevated by ConA *in vivo*, wherein the crossbars show the average of each group and p value was calculated by student's t-test.

Fig. 6 represents a photograph showing inhibition activities of the compound of the invention in apoptotic lesions and morphological, histological changes of hepatocytes in ConA-treated mouse liver.

Fig. 7 represents an electrophoresis image showing inhibition activities of the compound of the invention on PARP cleavage caused by ConA-induced apoptotic death of hepatocytes. Each lane is representative of 10 mice per group.

Fig. 8 is a graphical representation showing hepatic protection of the compound of the invention from IFN_{γ} and anti-Fas antibody-induced apoptosis.

Fig. 9 represents hepatic protection of the compound of the invention from anti-Fas antibody-induced apoptosis.

Fig. 10 is a graph showing inhibition activity of the compound of the invention against caspase-3-like activity in anti-Fas antibody-treated liver tissues.

Fig. 11 represents protection of mice by the compound of the invention from anti-Fas antibody-induced lethality.

Fig. 12 is a graphical representation showing the protection of mice liver by the compound of the invention from TNF_{α} -induced apoptosis.

Fig. 13 is a graphical representation showing that the compound of the invention inhibits caspase-3-like activity in TNF_{α} -treated liver.

Fig. 14 is a graphical representation showing that the compound of the invention protects mice from TNF_{α} -induced lethality.

Fig. 15 is a graphical representation showing that the compound of the invention inhibits TNF_{α} /Actinomycin D-induced caspase activation and apoptosis in primary cultured rat hepatocytes.

Fig. 16 is a graphical representation showing that the compound of the invention prevents hepatocyte apoptosis preinduced by TNF_{α} /Actinomycin D.

Fig. 17 is a graphical representation showing that the compound of the invention prevents TNF_{α} /DaIN-mediated mortality.

BEST MODE FOR CARRYING OUT THE INVENTION

In advance of illustrating the present invention in datail, some important terms are defined as follows:

a) Simple Alkyl Chain (hereinafter referred to as "SAC") is meant by a

carbohydrate having C_{1-8}, and contains a branched isomeric form.

b) Simple CycloAlkyl Chain (hereinafter referred to as "SCAC" is meant by a cyclic compound having C_{3-10}.

c) Aryl group (hereinafter referred to as "Ar") represents benzene [1:2,3,4,5,6], naphthalene[1,2:1,2,3,4,5,6,7,8,], pyridine [2,3,4:2,3,4,5,6], indole[1,2,3,4,5,6,7: 1,2,3,4,5,6,7], quinoline[2,3,4,5,6,7,8: 2,3,4,5,6,7,8], isoquinoline[1,3,4,5,6,7,8: 1,3,4,5,6,7,8], furan [2,3:2,3,4,5], thiophene[2,3:2,3,4,5], pyrole[1,2,3: 1,2,3,4,5], pyrimidine [2,4,5,6: 2,4,5,6], imidazole[1,2,4,5:1,2,4,5], benzofuran[2,3;2,3,4,5,6,7], etc. in which the former digits within the bracket represents a position where the corresponding aryl group is connected to the inhibitor according to the present invention and the latter digits after the colon represents a position where the substituent Y defined later can be attached.

d) Side chain of amino acids represents the side groups which are attached to the chiral carbon of 20 natural amino acids.

Frequently referred terms are abbreviated as follows:

N-chlorosuccinimide : NCS

N-methylmorporline : NMM

N,N-dimethyl formamide : DMF

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide: EDC

1-hydroxybenzotriazole hydrate : HOBt

Trifluoroacetic acid : TFA

t-butoxycarbonyl : Boc

benzyloxycarbonyl : Cbz

methyl : Me

ethyl : Et

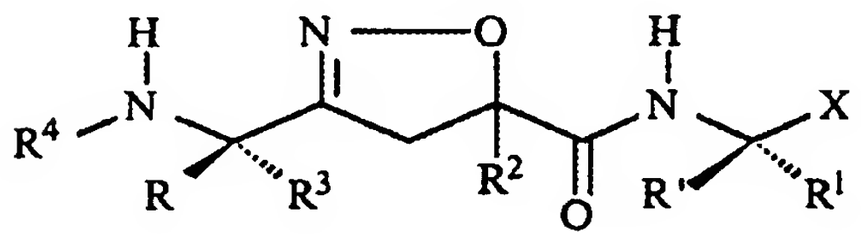
equivalent : Eq or eq

The term "stereochemically isomeric forms" as used in the foregoing and hereinafter defines all the possible isomeric forms which the derivative of formula (1) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes a mixture of all possible stereochemically isomeric forms, said mixture containing all diastereomers of the basic molecular structure. Stereochemically isomeric forms of the derivatives of the formula (1) are intended to be embraced within the scope of this invention.

The pharmaceutically acceptable salts as used in the foregoing and hereinafter comprises the therapeutically active non-toxic salt forms which can form the derivative of formula (1).

Hereinafter, the invention will be illustrated in more detail.

In one aspect, the present invention provides a novel isoxazoline derivative of the formula (I), the pharmaceutically acceptable salts, esters and stereochemically isomeric forms thereof.



(I)

In the compound of formula (I), the substituents are defined as follows:

R and R' each independently represents hydrogen, simple alkyl chain

(-SAC), simple cycloalkyl (-SCAC), aromatic (-Ar), or simple alkyl chain substituted with aromatic (-SAC-Ar); preferably represents hydrogen. Throughout the description of the specification, R' has the same meaning as R unless specifically defined.

R^1 represents -SAC, -SCAC, -Ar, or -SAC-Ar, or represents side chain of amino acids, or $-(CH_2)_nCOOZ$ (in which n is 1 or 2, and Z is hydrogen, -SAC, -Ar or -SCAC); preferably represents $-CH_2COOH$.

R^3 represents -SAC, -SCAC, -Ar, -SAC-Ar, or side chain of amino acids; preferably represents $-CH(CH_3)_2$, $-CH_2COOH$, $-(CH_2)_2CO_2H$, $-CH_2C(=O)NH_2$ or $-(CH_2)_2C(=O)NH_2$.

In a case where an adjacent position of R^1 or R^3 become a stereogenic center, both the stereoisomeric compounds are intended to be embraced within the scope of the present invention. Similarly, a case where two forms of compounds are co-exist (a mixture of diastereomeric compounds) is embraced within the scope of the invention. In addition, the cases where R^1 or R^3 are composed of carboxylic acids or bases with side chain residue of amino acids, their protected forms such as simple esters or pharmaceutically acceptable salt forms are also embraced within the scope of the compounds according to the invention.

R^2 represents -H, -SAC, -SCAC, -Ar, or -SAC-Ar, or represents side chain of amino acids, or represents $-(CH_2)_n(O)_mR^5$ (in which R^5 = -SAC, -SCAC, -Ar, -SAC-Ar; n=0, 1 or 2; and m=0 or 1), or $-(CH_2)_nOC(=O)R^6$ (in which R^6 = -SAC, -SCAC, -Ar, or -SAC-Ar; and n=1 or 2). Preferable R^2 represents $(CH_2)_n(O)_mAr'$ (in which n=0, 1, or 2; and m = 0 or 1; Ar' = substituted phenyl or imidazole), methyl or hydrogen.

In a case where an adjacent position due to R^2 become a stereogenic center, both the stereoisomeric compounds are embraced within the context of the compounds of the present invention, Similarly, a case where two forms of compounds are co-exist (a mixture of diastereomeric compounds) is embraced within the category of the compounds according to the invention. In addition, the cases where R^2 are composed of carboxylic acids or bases with side chain residue of amino acid, their protected forms such as simple esters or pharmaceutically acceptable salt forms are also embraced within the scope of the compounds according to the invention.

R^4 represents

a) amino acid residue in which ① the carboxyl group attached to the chiral carbon of amino acid is bound to the amine group to form an amide bond, ② the chiral carbon of amino acid has either R or S configuration, ③ the amino group attached to the chiral carbon of amino acid is protected by formyl, acetyl, propyl, cyclopropylcarbonyl, butyl, methanesulfonyl, ethanesulfonyl, propanesulfonyl, butanesulfonyl, methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, butyloxycarbonyl, methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, butylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, dibutylcarbamoyl or cyclopropylaminocarbonyl, or the amino group may be replaced with a hydrogen atom, and ④ the carboxyl group in the side chain may form an ester group with -SAC or -SCAC,

b) $-C(=O)R^7$ (in which R^7 = -SAC, -SCAC, -Ar, -SAC-Ar), $-CO_2R^8$ (in which R^8 = hydrogen or R^7), $-C(=O)NR^8R^8$, $-SOR^7$, $-SO_2R^7$, or $-C(=O)CH=CH-Ar$,

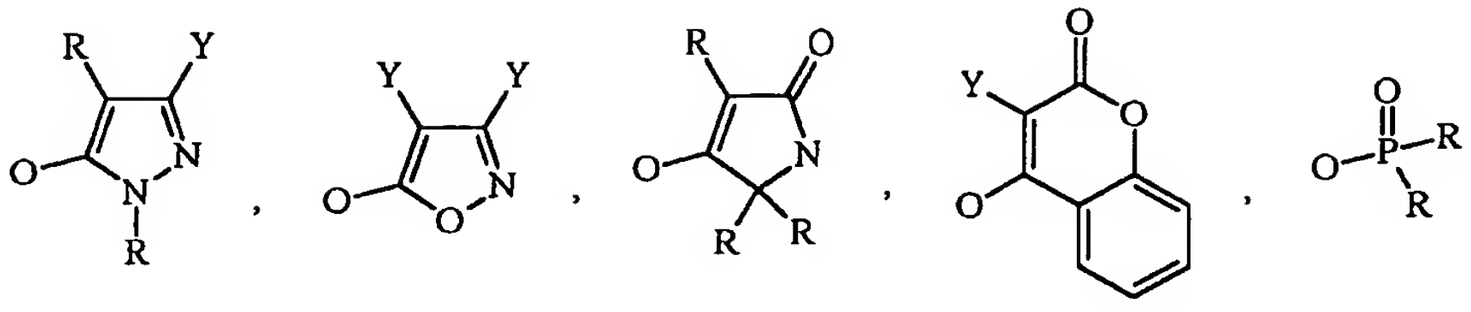
c) $-(C=O)-L-CO_2R^8$, in which L represents a divalent (=capable of double substitution) linker selected from a group consisting of C_{1-6} alkyl,

C_{3-8} cycloalkyl, furan, thiophene, diazole (1,2 or 1,3), triazole (1,2,3 or 1,3,4), tetrazole, oxazole, isoxazole, thiazole, isothiazole, diazine (1,2 or 1,3 or 1,4), triazine, -Ph(-R^9)- (in which R^9 = H, F, Cl, Br, I, CHO, OH, OCH_3, CF_3, OCF_3, CN, C(=O)Me), tetrahydrofuran, tetrahydrothiophene, 1,4-dioxane, -CH=C(R^{10})- (in which R^{10}=H, methyl, ethyl), -CH=CHCH(R^{10})- , -CH(OR^{10})CH_2-, -CH_2C(=O)CH_2-, -C(=O)CH_2CH_2-

In cases where R^1 and the adjacent R', and/or R^3 and the adjacent R are connected to each other to form a cyclic compound, R^1-R' or R^3-R together represents -$(CH_2)_n$-, -$(CH_2)_n$-O-$(CH_2)_m$-, or -$(CH_2)_n$-NR^{13}-$(CH_2)_m$- (in which n+m<9, R^{13}=-SAC, -SCAC, -Ar, -SAC-Ar, -C(=O)-SAC, -C(=O)-SCAC, -C(=O)-Ar, or -C(=O)-SAC-Ar);

X represents -CN, -CHO, -C(=O)R^{14} (in which R^{14} = -SAC, -SCAC, -Ar, -SAC-Ar, or -CHN_2), -C(=O)OR^{15} (in which R^{15} = -SAC, -SCAC, -Ar, or -SAC-Ar), -CO$NR^{16}R^{17}$ (in which R^{16} and R^{17} each represents -H, -SAC, -O-SAC, -SCAC, -Ar, or -SAC-Ar), -C(=O)CH_2O(C=O)Ar" (in which Ar" = 2,6-disubstituted phenyl with F, Cl, Br, I, or CH_3), -C(=O)$CH_2O$$R^{18}$ (in which R^{18} represents -SAC, -SCAC, -Ar, or -SAC-Ar), or -C(=O)CH_2OC(=O)R^{19} (in which R^{19} = -SAC, -SCAC, -Ar, or -SAC-Ar), or

X represents -$COCH_2$-W, wherein W represents -N_2, -F, -Cl, -Br, -I, -$NR^{20}R^{21}$ or -SR^{22} (in which wherein R^{20}, R^{21} and R^{22} each independently represents -SAC, -SCAC, -Ar, or -SAC-Ar or R^{20} and R^{21} are connected to form a cyclic compound); or W represents



in which Y represents -OH, OR^{23} (in which R^{23} = -SAC, or -SCAC), $-C(=O)R^{24}$ (in which R^{24} = -H, -SAC, or -SCAC), -F, -Cl, -Br, -I, -CN, -NC, $-N_3$, $-CO_2H$, $-CF_3$, $-CO_2R^{25}$ (in which R^{25} = -SAC, or -SCAC), $-C(=O)NHR^{26}$ (in which R^{26} = -SAC, or -SCAC), and $-C(=O)NR^{27}R^{28}$ (in which R^{27}, R^{28} = -SAC, or -SCAC) and can be mono- or poly-substituted at its maximum regardless of the order and the kinds.

Among the compound of formula (I), preferred are those in which R^4 represents $-C(=O)(CH_2)_pCOOZ$ (in which p is 1 to 4, and Z is hydrogen, -SAC, -Ar or -SCAC). Also preferred are those in which R^1 represents $-(CH_2)_nCOOZ$ (in which n is 1 or 2, and Z is hydrogen, -SAC, -Ar or -SCAC).

Among the compound of formula (I), more preferred are those in which

a) R and R' represent hydrogen,

b) R^1 represents $-CH_2COOH$, $-CH_2COOCH_3$, or $CH_2COOCH_2CH_3$,

c) R^2 represents $-(CH_2)_n(O)_mR^5$ (in which R^5 = -SAC, -SCAC, -Ar, -SAC-Ar; n=0, 1 or 2; and m=0 or 1), SAC, Ar, or Hydrogen,

d) R^3 represents $-CH(CH_3)_2$, $-CH_2COOH$, $-(CH_2)_2CO_2H$, $-CH_2C(O)NH_2$ or $-(CH_2)_2C(O)NH_2$,

e) R^4 represents $-C(=O)(O)_nR^{29}$ (in which n=0, 1; R^{29}= -Ar or -SAC-Ar), $-SO_2R^{30}$ (in which R^{30}= -Ar or -SAC-Ar), or $-C(=O)NHR^{31}$ (in which R^{31} = -Ar, or -SAC-Ar), or

f) X represents $-C(=O)CHN_2$, $-C(=O)CH_2Br$, $-C(=O)CH_2Cl$, $-C(=O)CH_2OPh$

or -C(=O)CH_2OC(=O)Ar" (in which Ar"=2,6-dichlorophenyl, 2,6-difluorophenyl or 2,6-dimethylphenyl).

Most preferred compounds are selected from the group consisting of the following:

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid;

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-pentanoic acid;

(2S)-2-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-succinic acid 1-(N-methyl-N-methoxy)-amide;

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-1-carbonylamino)-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid(LP and MP);

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid(LP and MP);

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid(LP and MP);

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-3-carboxy-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[(1S)-1-(quinoline-2-yl-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-sulfonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2-naphthyloxy)-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(1-naphthyloxy)-pentanoic acid;

(3S)-3-{3-[(1S)-1-(2S)-2-acetylamino-succinoylamino)-3-carboxy-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-4,5-dihydro-

isoxazole-5-carbonylamino}-4-keto-5-(2-naphthyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(2-naphthalenecarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (diasteromeric mixture);
(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(phenylethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(phenylethylcarbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(phenylethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenecarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenecarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenecarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoylo xy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(1-naphtalenesulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid

(diastereomeric mixture);
(3S)-3-{3-[2-methyl-(1S)-1-(1-naphtalenesulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid (diastereomeric mixture);
(3S)-3-{3-[2-methyl-(1S)-1-(1-naphtalenesulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid (diastereomeric mixture);
(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)ethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)ethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)ethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)methylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)methylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)methylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(cinnamoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(cinnamoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(cinnamoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-

pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethylsulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethylsulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethylsulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-(1-

imidazolyl-methyl)-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(2-naphthalenecarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid;

(3S)-3-{3-[(1S)-1-(succinoylamino)-3-carboxy-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(1-piperidinyl)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(isoquinoline-1-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(isoquinoline-3-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-4-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(benzofuran-2-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-1-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-difluorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-3-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)- pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-1-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dimethylbenzoyloxy)-pentanoic acid[diastereomeric mixture];

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-8-carbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid [diastereomeric mixture];

(3S)-3-{3-[2-methyl-(1S)-1-(indole-2-carbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(indole-3-carbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-1-carbonylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(benzofuran-2-carbonylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[3-carboxy-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-propyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(N-piperidine)-pentanoic acid[diastereomeric mixture];

(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(N-pyrrolidine)-pentanoic acid

[diastereomeric mixture];
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-butyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2-naphthyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-propyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid [diastereomeric mixture];
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-hydroxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid [diastereomeric mixture];
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methoxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid [diastereomeric mixture];
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-n-pentyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-ethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(glutaroylamino)-propyl]-5-methyl-4,5-dihydro-iso-xazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
and
(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid methyl ester.

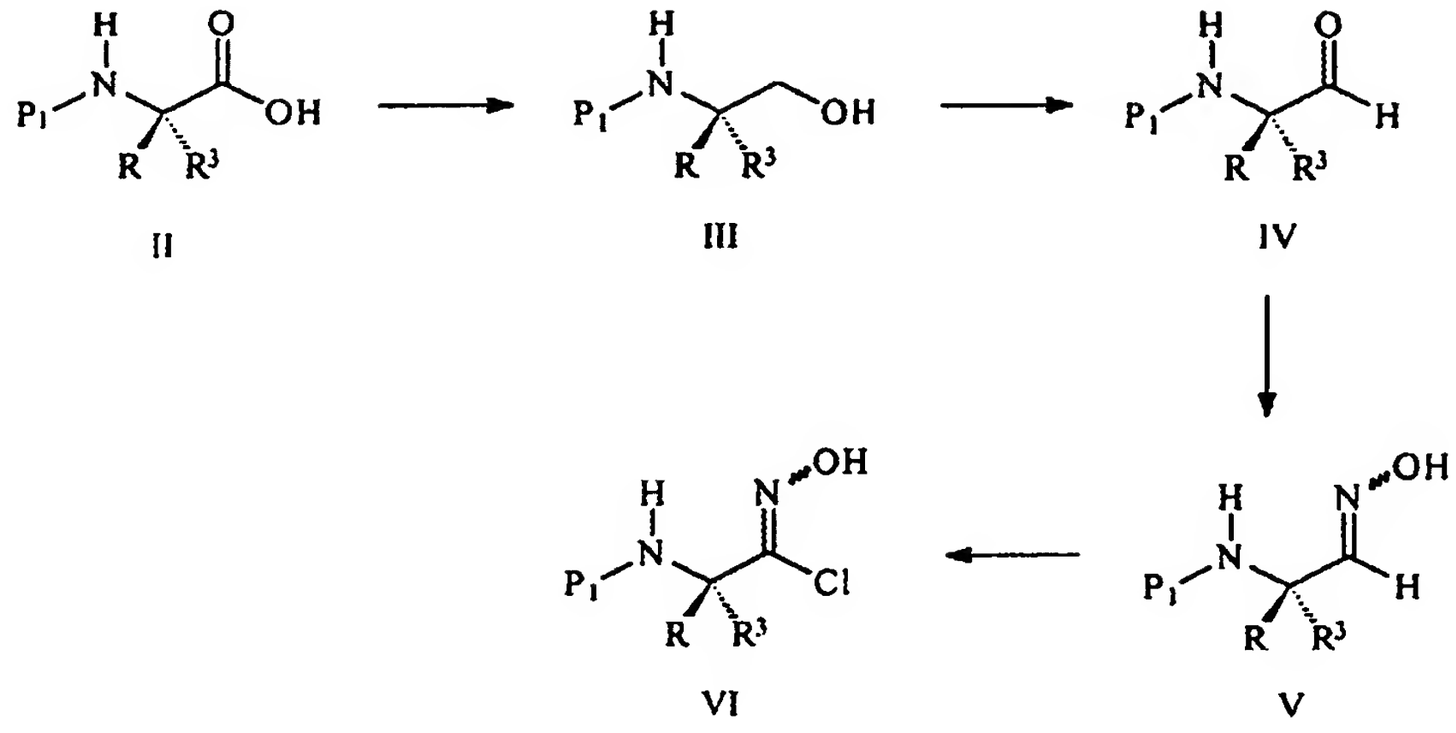
In another aspect, the present invention provides a process for preparing a compound of formula (I).

Hereinafter, a process for preparing the isoxazoline derivatives of formula (I) according to the present invention will be explained with respect to Reaction Schemes 1 and 2. It should be understood that the reaction schemes generally illustrate the specific process used in the present invention, but any modification of the unit operations may be made without departure of the spirit of the invention. Therefore, the present invention should not be limited to the following preferred embodiments.

In the first step, amino protected amino acid (II) (commerically available from Novabiochem) is reduced to give N-protected amino alcohol (III) which is then oxidized to give N-protected amino aldehyde (IV).

N-protected amino aldehyde (IV) is reacted with hydroxylamine-hydrochloride and sodium carbonate in a mixed solution of an alcohol and water to give an oxime (V) (syn- and anti-oxime). The resulting oxime derivative (V) is treated with NCS (N-chlorosuccinimide) in an aqueous solution of dimethylformamide to give hydroxamoyl chloride (VI). As the representative substituents used in the synthesis of hydroxamoyl chloride, the following groups may be exemplified: P_1 represents Cbz, t-Boc, Fmoc, Teoc(trimethylsilyl-ethyloxycarbonyl), etc.; R represents H and R^3 represents $-CH_2CH_2CO_2Bu(t)$, $-CH_2CO_2Me$, $-CH_2CO_2Bu(t)$, -isopropyl, phenylmethyl, and the like.

Reaction Scheme 1



In the above Reaction Scheme 1, the following combinations of a) to g) for the commercially available compounds (II) to (VI) may be synthesized.

a) P_1 = Cbz, R = H, R^3 = i-Pr

b) P_1 = t-Boc, R = H, R^3 = i-Pr

c) P_1 = Fmoc, R = H, R^3 = $CH_2CH_2CO_2Bu(t)$

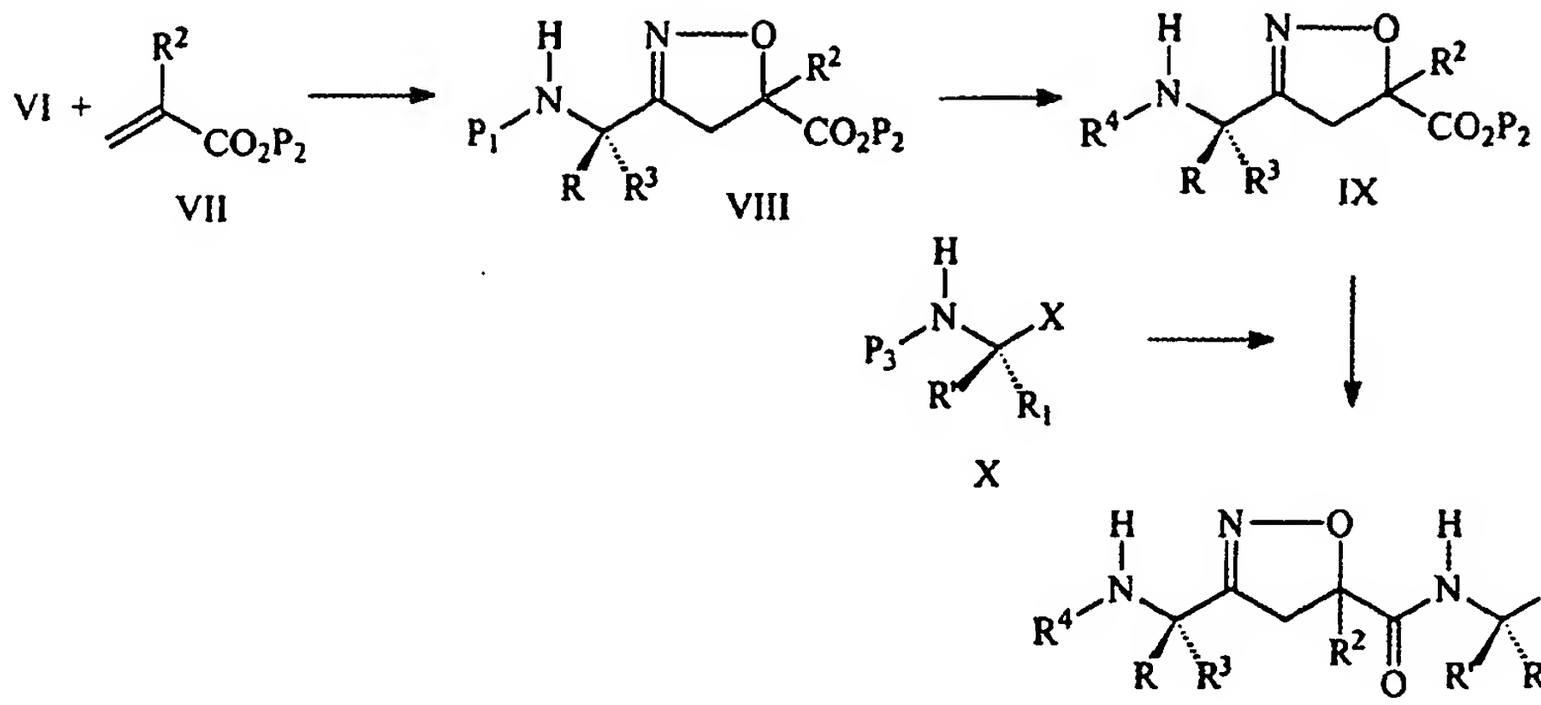
d) P_1 = t-Boc, R = H, R^3 = CH_2CO_2Me

e) P_1 = Cbz, R = H, R^3 = $CH_2CO_2Bu(t)$

f) P_1 = Fmoc, R = H, R^3 = $CH_2CO_2Bu(t)$

g) P_1 = Boc or Cbz, R = H, R^3 = CH_2Ph

Reaction Scheme 2



I

In the second step, the hydroxamoyl chloride (VI) thus obtained is then reacted with acrylate derivative (VII) to give isoxazoline derivative (VIII). If necessary, isoxazoline derivative (VIII) may be synthesized directly from the oxime derivative (V).

If a compound having the protecting group P_1 can be used as the inhibitor (for example, P_1 is a Cbz group), the isoxazoline derivative (VIII) is directly reacted with the compound (X) to give a compound of formula (I), and there is need to convert the protecting group P_1 into other substituent, P_1 is removed and R^4 is introduced thereinto.

In the above Reacion Scheme 2, the following combination of substituents may be synthesized.

In the compound (VIII),

a) P_1 = Cbz, R = H, R^3 = i-Pr, R^2 = H, P_2 = Et

b) P_1 = Cbz, R = H, R^3 = i-Pr, R^2 = H, P_2 = H

c) P_1 = Cbz, R = H, R^3 = i-Pr, R^2 = CH_2OPh, P_2 = Et

d) P_1 = Cbz, R = H, R^3 = i-Pr, R^2 = CH_2OPh, P_2 = H

e) P_1 = Fmoc, R = H, R^3 = $CH_2CH_2CO_2Bu(t)$, R^2 = CH_3, P_2 = CH_3(or Et)

f) P_1 = Teoc, R = H, R^3 = i-Pr, R^2 = CH_3, P_2 = H

g) P_1 = t-Boc, R = H, R^3 = i-Pr, R^2= $PhCH_2$, P_2=Et

h) P_1 = t-Boc, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, P_2 = Et

i) P_1 = t-Boc, R = H, R^3 = i-Pr, R^2 = 1-naphthyl, P_2 = Et

j) P_1 = t-Boc, R = H, R^3 = i-Pr, R^2 = 2-naphthyl, P_2 = Et

k) P_1 = t-Boc, R = H, R^3 = i-Pr, R^2 = phenyl, P_2 = Et

l) P_1 = t-Boc, R = H, R^3 = i-Pr, R^2 = 4-bromophenyl, P_2 = Et

m) P_1 = t-Boc, R = H, R^3 = i-Pr, R^2 = $AcOCH_2$, P_2 = Et

In the compound (IX),

a) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = H, P_2 = Et

b) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = H, P_2 = H

c) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = CH_2OPh, P_2 = Et

d) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = CH_2OPh, P_2 = H

e) R^4 = 1-naphthoyl, R = H, R^3 = i-Pr, R^2 = CH_2OPh, P_2 = Et

f) R^4 = 1-naphthoyl, R = H, R^3 = i-Pr, R^2 = CH_2OPh, P_2 = H

g) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = CH_2OPh, P_2 = Et

h) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = CH_2OPh, P_2 = H

i) R^4 = 2-naphthoyl, R = H, R^3 = $CH_2CH_2CO_2Bu(t)$, R^2 = CH_3, P_2 = CH_3

j) R^4 = 2-naphthoyl, R = H, R^3 = $CH_2CH_2CO_2Bu(t)$, R^2 = CH_3, P_2 = H

k) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = Et

l) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = H

m) R^4 = 2-naphthalenesulfonyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, P_2 = Et

n) R^4 = 2-naphthalenesulfonyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, P_2 = H

o) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, P_2 = Et

p) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, P_2 = H

q) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = H, P_2 = Et

r) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = H, P_2 = H

s) R^4 = hydrocinnamoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = Et

t) R^4 = hydrocinnamoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = H

u) R^4 = 1-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = Et

v) R^4 = 1-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = H

w) R^4 = 1-naphthalenesulfonyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = Et

x) R^4 = 1-naphthalenesulfonyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = H

y) R^4 = 3-indoleacetyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = Et

z) R^4 = 3-indoleacetyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = H

aa) R^4 = 3-indolepropionyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = Et

ab) R^4 = 3-indolepropionyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = H

ac) R^4 = *trans*-cinnamoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = Et

ad) R^4 = *trans*-cinnamoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = H

ae) R^4 = phenylmethylsulfonyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = Et

af) R^4 = phenylmethylsulfonyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = H

ag) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = H, P_2 = Et

ah) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = H, P_2 = H

ai) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = Et

aj) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = H

ak) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = 1-imidazolyl, P_2 = Et

al) R^4 = 1-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = 1-imidazolyl, P_2 = H

am) R^4 = $COCH_2CH_2CO_2Bu(t)$, R = H, R^3 = $CH_2CH_2CO_2Bu(t)$, R^2 = CH_3, P_2 = CH_3

an) R^4 = $COCH_2CH_2CO_2Bu(t)$, R = H, R^3 = $CH_2CH_2CO_2Bu(t)$, R^2 = CH_3, P_2 = H

ao) R^4 = $COCH_2CH_2CO_2Bu(t)$, R = H, R^3 = i-Pr, R^2 = CH_3, P_2 = CH_3

ap) R^4 = $COCH_2CH_2CO_2Bu(t)$, R = H, R^3 = i-Pr, R^2 = CH_3, P_2 = H

In the compound (X),

a) P_3 = Cbz, R = H, R^1=$CH_2CO_2Bu(t)$, X =CO_2Me

b) P_3 = HCl+H, R = H, R^1=$CH_2CO_2Bu(t)$, X =CO_2Me

c) P_3 = Cbz, R = H, R^1=$CH_2CO_2Bu(t)$, X =$COCH_2N_2$

d) P_3 = Cbz, R = H, R^1=$CH_2CO_2Bu(t)$, X =$COCH_2Br$

e) P_3 = Cbz, R = H, R^1=$CH_2CO_2Bu(t)$, X =$COCH_2OPh$

f) P_3 = Cbz, R = H, R^1=$CH_2CO_2Bu(t)$, X =$CH(OH)CH_2OPh$

g) P_3 = H, R = H, R^1=$CH_2CO_2Bu(t)$, X =$CH(OH)CH_2OPh$

h) P_3 = Cbz, R = H, R^1=$CH_2CO_2Bu(t)$,

X = $CH(OH)CH_2OC(O)Ph$(2,6-dichloro)

i) P_3 = H, R = H, R^1=$CH_2CO_2Bu(t)$,

X =$CH(OH)CH_2OC(O)Ph$(2,6-dichloro)

j) P_3 = Cbz, R = H, R^1=$CH_2CO_2Bu(t)$, X =CONMe(OMe)

k) P_3 = H, R = H, R^1=$CH_2CO_2Bu(t)$, X =CONMe(OMe)

l) P_3 = Cbz, R = H, R^1=$CH_2CO_2Bu(t)$, X =$CH(OH)CH_2O$- (1-naphthyl)

m) P_3 = H, R = H, R^1=$CH_2CO_2Bu(t)$, X =$CH(OH)CH_2O$- (1-naphthyl)

In the compound (I),

a) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = CO_2H

b) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2N_2$

c) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2Br$

d) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OPh$

e) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)Ph$ (2,6-dichloro)

f) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = 2-naphthyloxymethylcarbonyl

g) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = 1-naphthyloxymethylcarbonyl

h) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $CH(OH)CH_2OPh$

i) R^4 = 1-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OPh$

j) R^4 = 2-naphthalenesulfonyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $CH(OH)CH_2OPh$

k) R^4 = 2-naphthalenesulfonyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OPh$

l) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $CH(OH)CH_2OPh$

m) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $CH(OH)CH_2OPh$

n) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2N_2$

o) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2Br$

p) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OPh$

q) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)$-Ph-(2,6-dichloro)

r) R^4 = N-acetyl-β -t-butyl aspartyl, R = H, R^3 = $CH_2CH_2CO_2Bu(t)$, R^2 = CH_3, R^1 = $CH_2CO_2Bu(t)$, X = $CH(OH)CH_2OPh$

s) R^4 = N-acetyl-β -t-butyl aspartyl, R = H, R^3 = $CH_2CH_2CO_2Bu(t)$, R^2 = CH_3, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OPh$

t) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = H, R^1 = $CH_2CO_2Bu(t)$, X =

C(=O)NMe(OMe)

u) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = H, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_3$

v) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = CO_2CH_3

w) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = CO_2H

10x) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2N_2$

y) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2Br$

z) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)$-Ph-2,6-dichloro

aa) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = C(=O)NMe(OMe)

ab) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_3$

ac) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = H, R^1 = $CH_2CO_2Bu(t)$, X = CO_2CH_3

ad) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = H, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)Ph(2,6\text{-dichloro})$

ae) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = H, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OPh$

af) R^4 = hydrocinnamoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)Ph(2,6\text{-dichloro})$

ag) R^4 = 1-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)Ph(2,6\text{-dichloro})$

ah) R^4 = 1-naphthalenesulphonyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)Ph(2,6\text{-dichloro})$

ai) R^4 = 3-indoleacetyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)Ph(2,6\text{-dichloro})$

aj) R^4 = 3-indolepropionyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)Ph(2,6\text{-dichloro})$

ak) R^4 = *trans*-cinnamoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)Ph(2,6\text{-dichloro})$

al) R^4 = phenylmethylsulfonyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)Ph(2,6\text{-dichloro})$

am) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = H, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)Ph(2,6\text{-dichloro})$

an) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = H, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OPh$

ao) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)Ph(2,6\text{-dichloro})$

ap) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OPh$

aq) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = 1-imidazolyl, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OCPh$

ar) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = H, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_3$

as) R^4 = $COCH_2CH_2CO_2Bu(t)$, R = H, R^3 = ($CH_2CH_2CO_2Bu(t)$, R^2 = CH_3, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OPh$

at) R^4 = $COCH_2CH_2CO_2Bu(t)$, R = H, R^3 = i-Pr, R^2 = CH_3, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OPh$

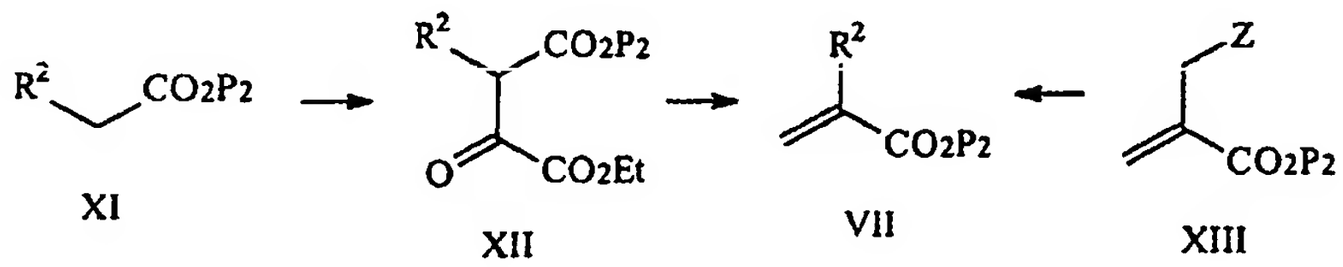
au) R^4 = 1-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2N(CH_2)_5$

In Reaction Scheme 2, the functional group X of compound (X) may be introduced by several unit operations after the reactions involved in the

synthesis of the compound (VIII) or (IX), or the compound (VIII) or (IX) already having desired substituent X may be proceed with the subsequent reactions.

The acrylate derivative (VII) may be synthesized by any one of two processes as depicted in Reaction Scheme 3 below.

Reaction Scheme 3



Ester derivative (XI) is reacted with diethyl oxalate to give oxalate derivative (XII) which is then reacted in the presence of a base to give desired acrylate derivative (VII). Alternatively, it may be synthesized by various processes starting from the known compound (XIII). That is, the known compound (XIIIa) is easily converted into compounds (XIIIb), (VIIe), (VIIf), (VIIg), etc.

In the compounds (XI) and (XII), the substituents are examplified as follows:

a) P_2 = Et, R^2 = Ph

b) P_2 = Et, R^2 = 4-bromophenyl

c) P_2 = Et, R^2 = 1-naphthyl

d) P_2 = Et, R^2 = 2-naphthyl

In the compounds (VII) and (XIII), the following combination of the substituents can be synthesized by the above process.

In the compound of (VII),

a) R^2 = Ph, P_2 = Et

b) R^2 = 4-bromophenyl, P_2 = Et

c) R^2 = 1-naphthyl, P_2 = Et

d) R^2 = 2-naphthyl, P_2 = Et

e) R^2 = CH_2OAc, P_2 = Et

f) R^2 = CH_2Ph, P_2 = Et

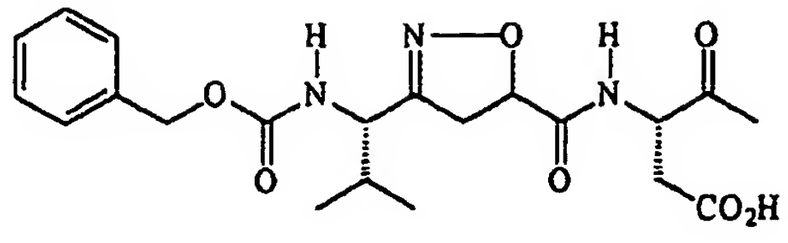
g) R^2 = CH_2OPh, P_2 = Et

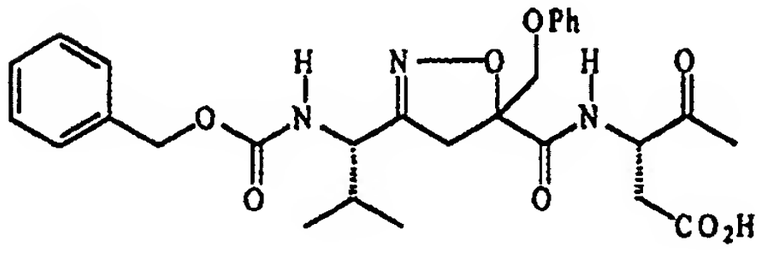
In the compound (XIII),

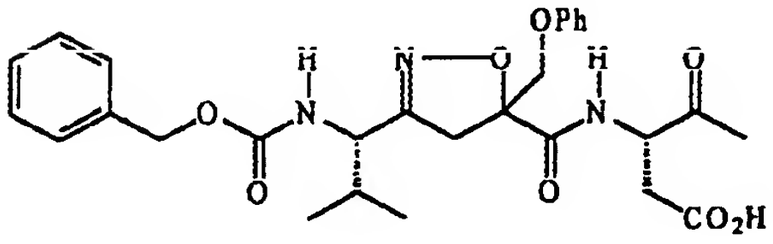
a) R^2 = Et, Z = OH

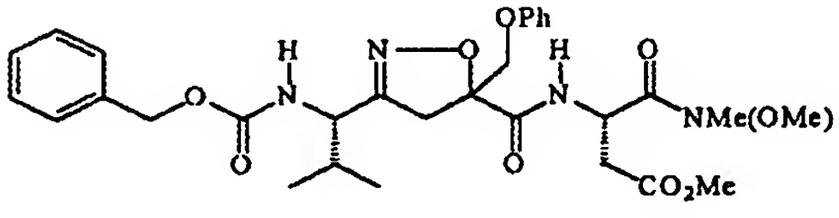
b) R^2 = Et, Z = Br

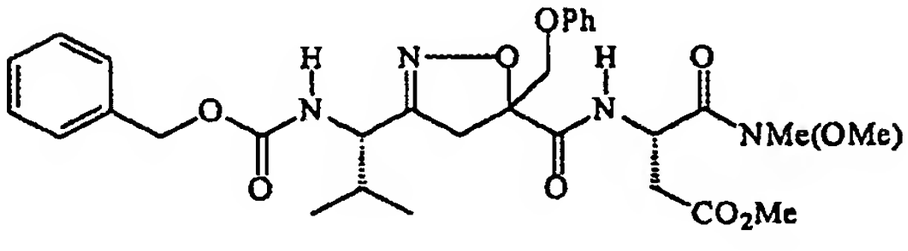
Hereinafter, the representative compounds synthesized by the process of the invention will be listed according to their structural formulae. The representative compounds according to the invention are numbered by the inventors for convenience' sake in which MP represents more polar fractions from HPLC at the previous step of deprotection while LP represents less polar fractions from HPLC. However, they are presented for the purpose of illustration of the synthesis of the compounds of the invention and for substantiating the fact that the compounds of the invention can be synthesized by the above mentioned process, but the present invention should not be limited to the listed compounds in any manner.

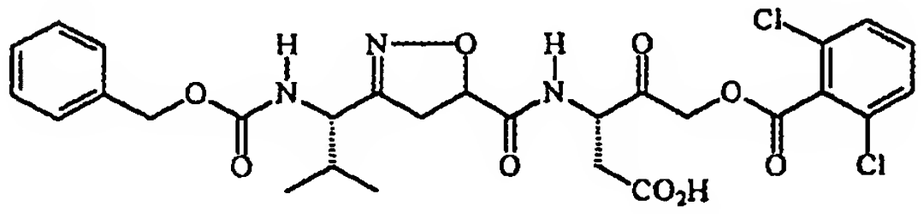
(3)  Diastereomer

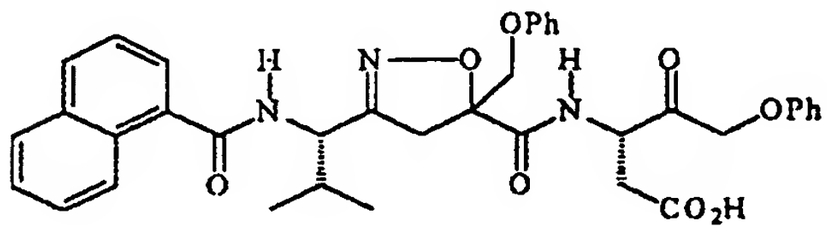
(10)  Diastereomer (less polar)

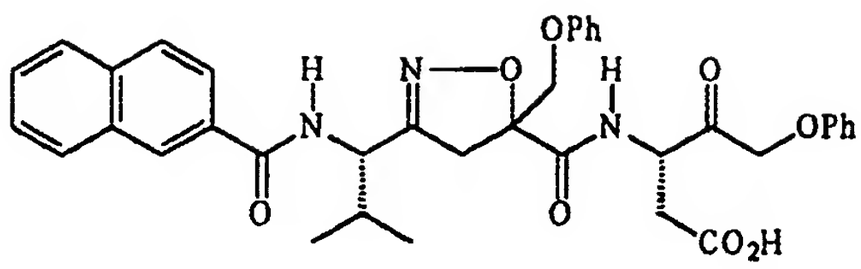
(11)  Diastereomer (more polar)

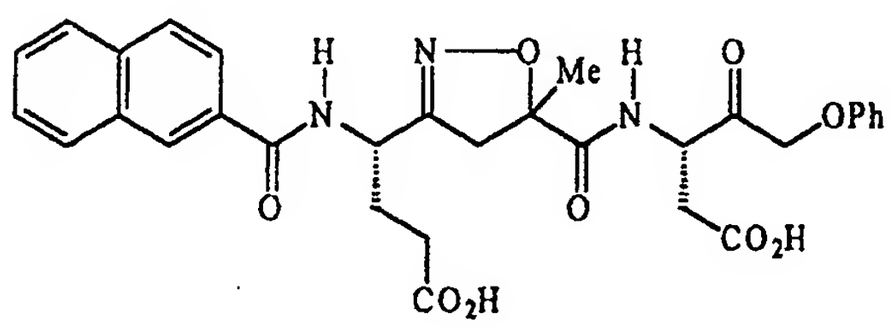
(12)  Diastereomer (less polar)

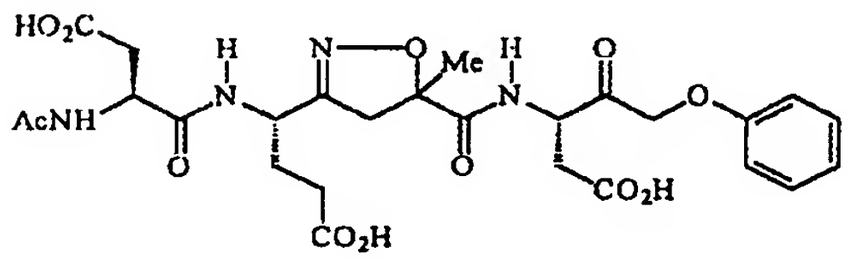
(13)  Diastereomer (more polar)

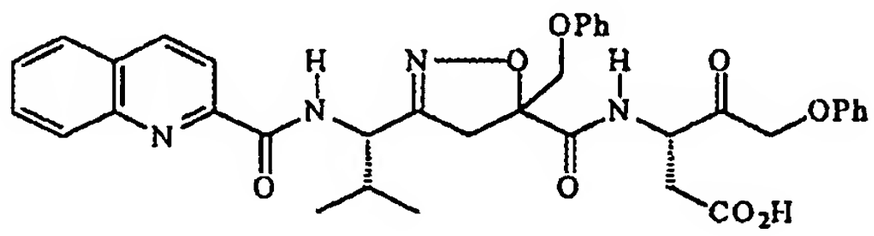
(14)  Diastereome

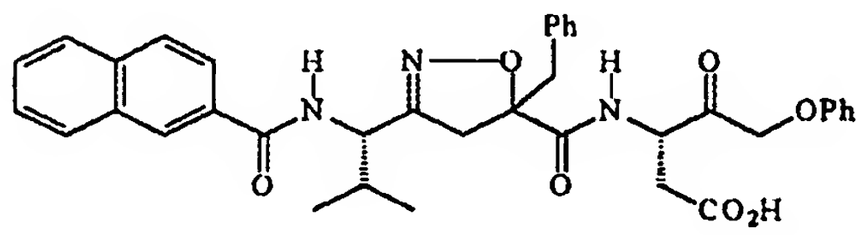
(17)  Diastereomer

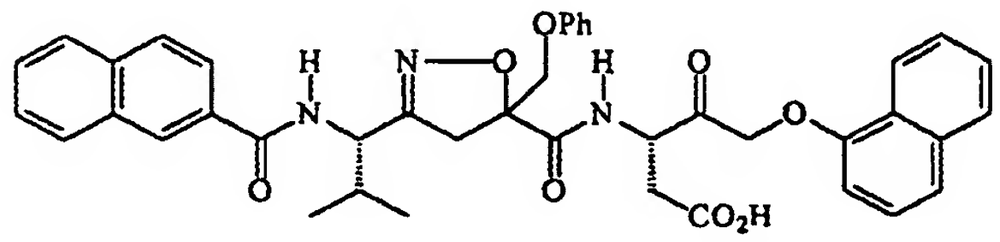
(18)  Stereoisomer

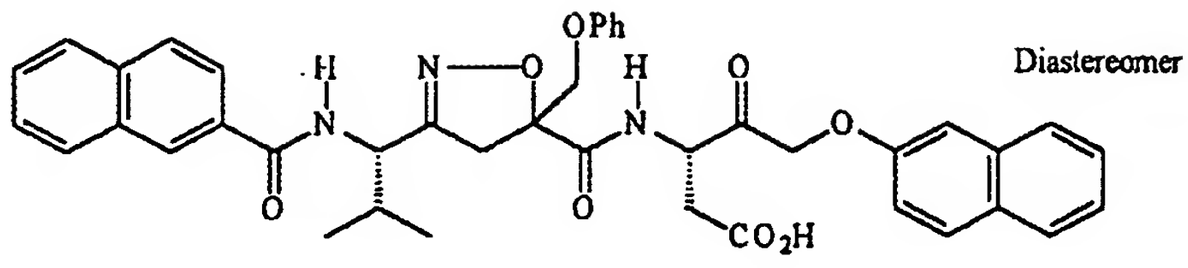
(19)  Diastereomer

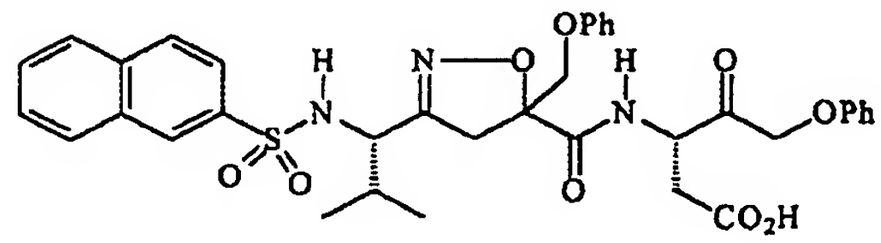
(20)  Diastereomer

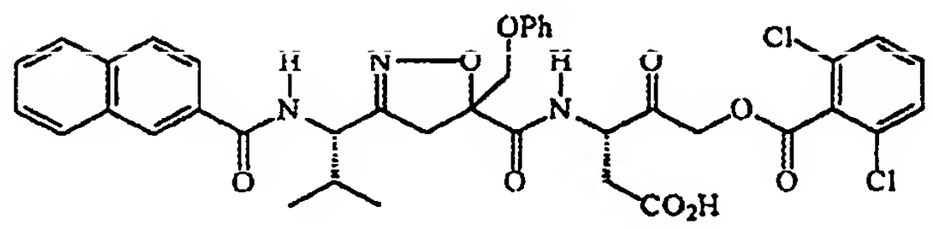
(22)  Diastereomer

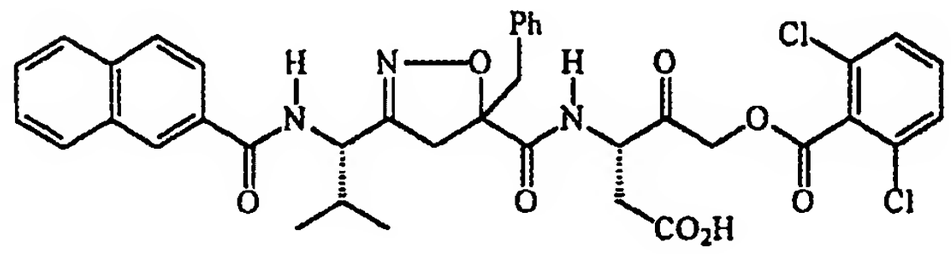
(23)  Stereoisomer

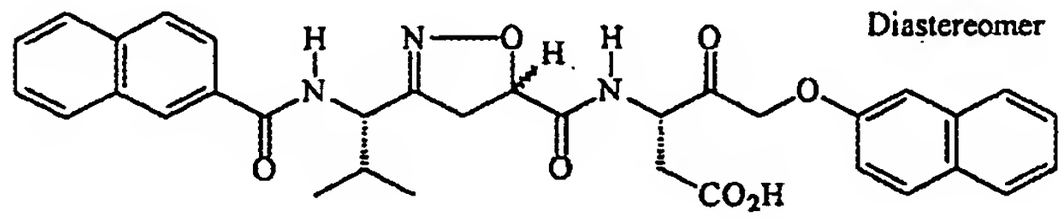
(24)  Diastereomer

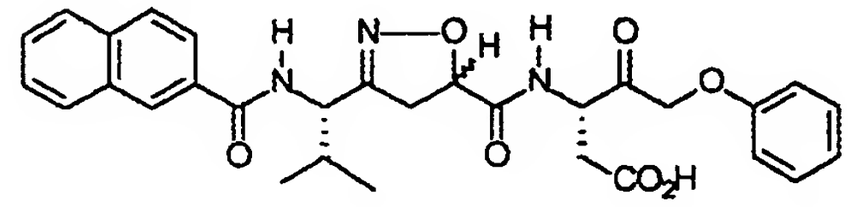
(25) 
Diastereomer

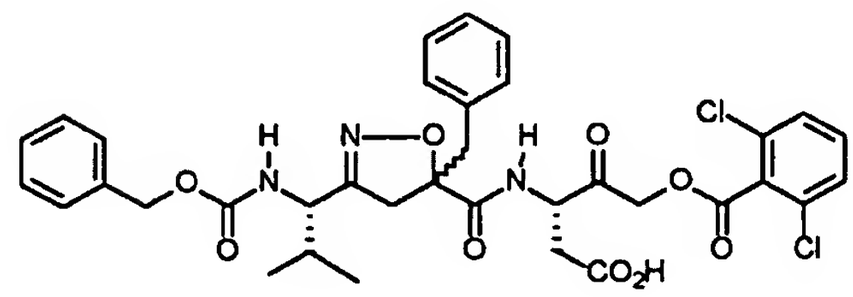
(26) 
Diastereomer

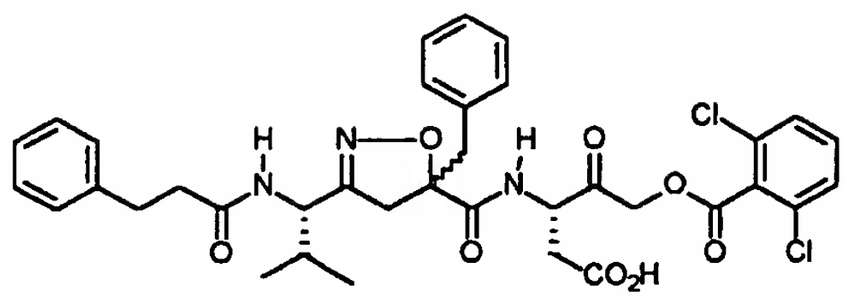
(27) 
Stereoisomer

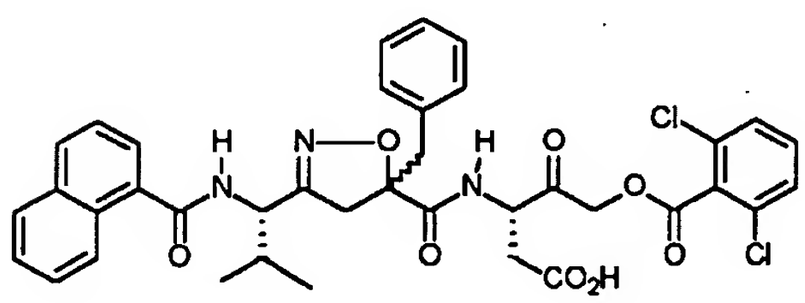
(28) 
Stereoisomer

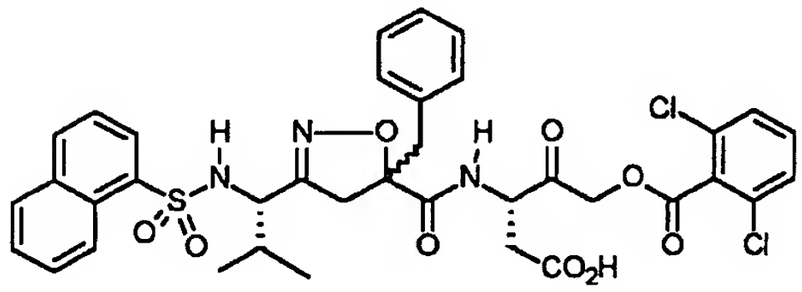
(29) 
Diastereomer

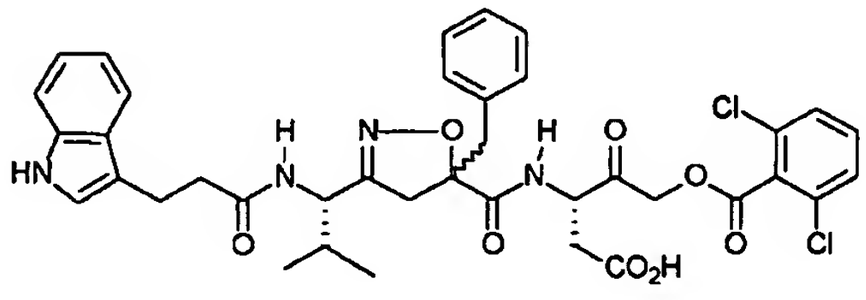
(30) 

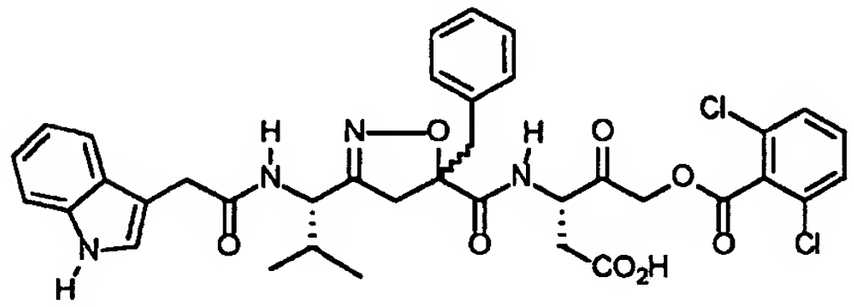
(31) 

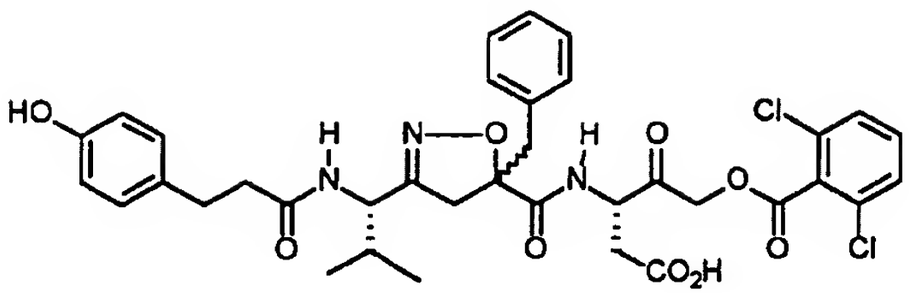
(32) 

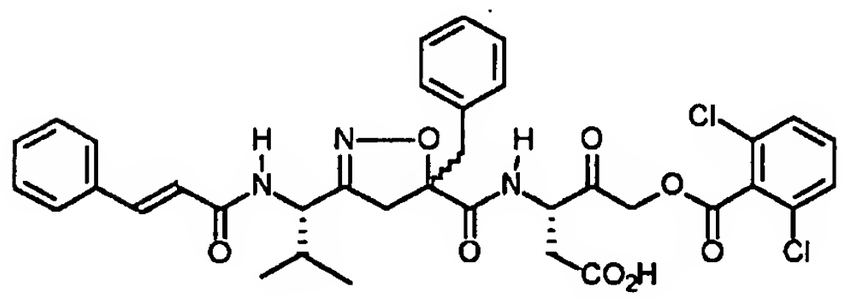
(33) 

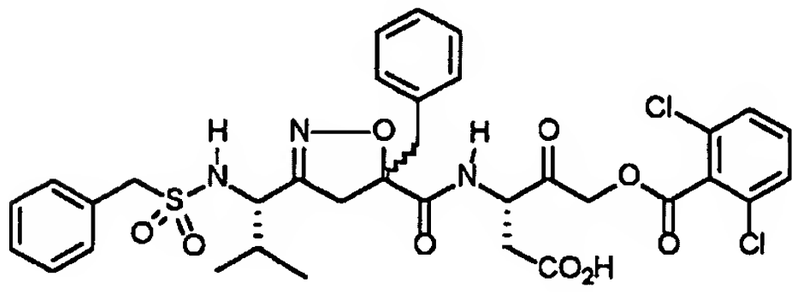
(34) 

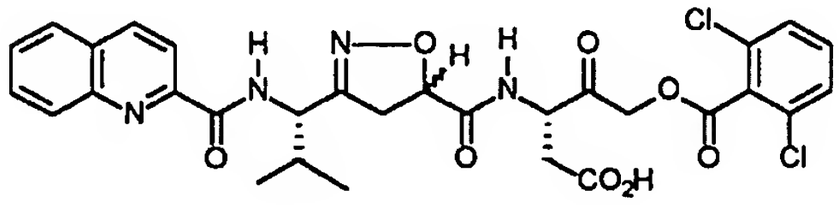
(35) 

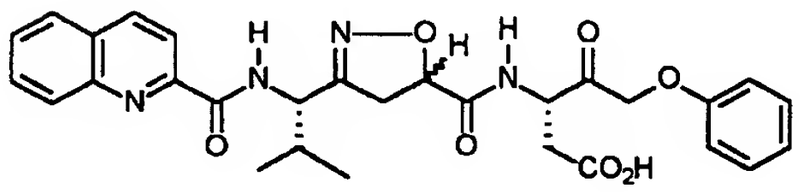
(36) 

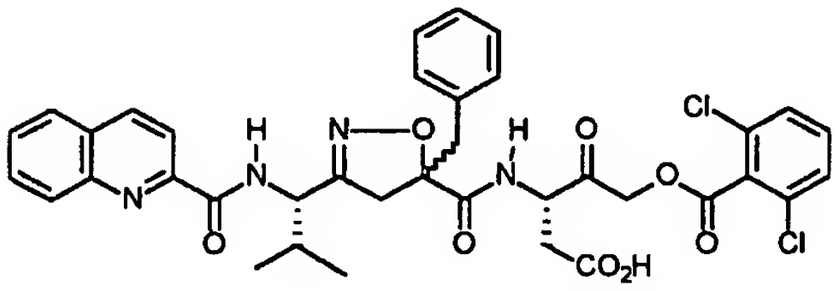
(37) 

(38) 

(39) 

(40) 

(41) 

(42) 

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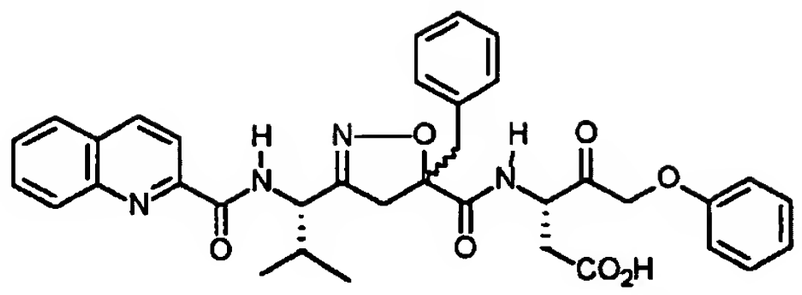

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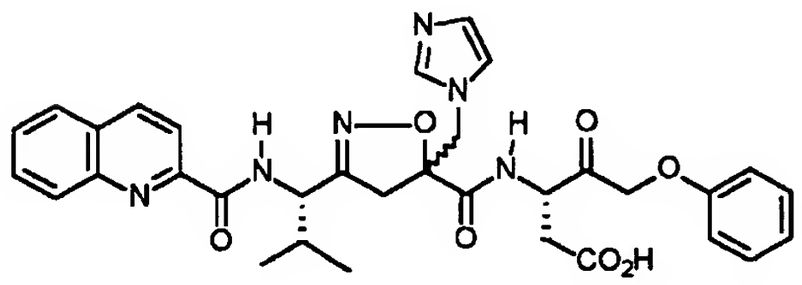

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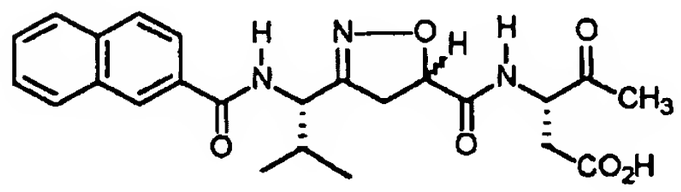

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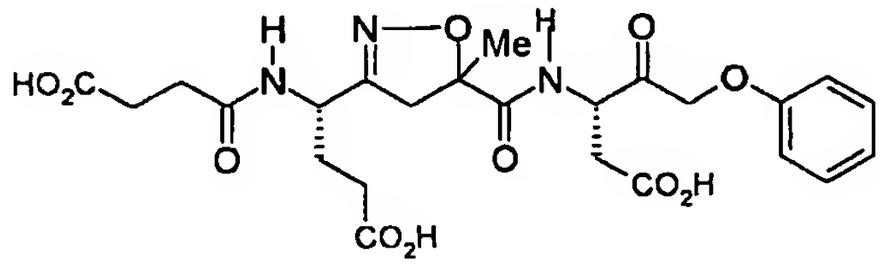

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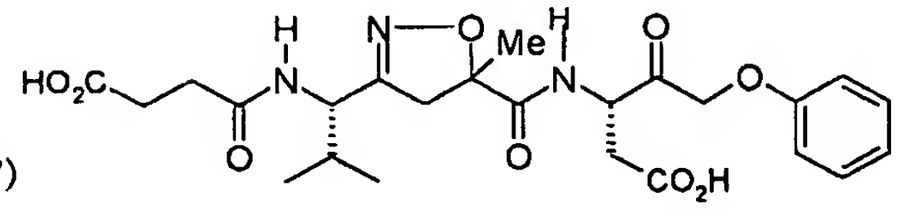

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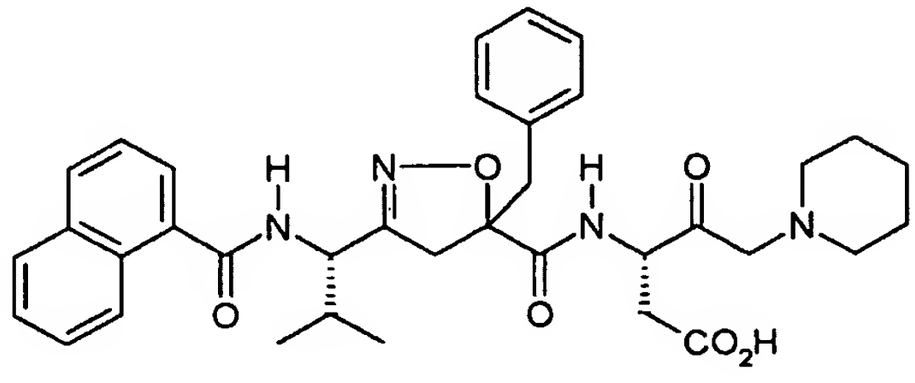
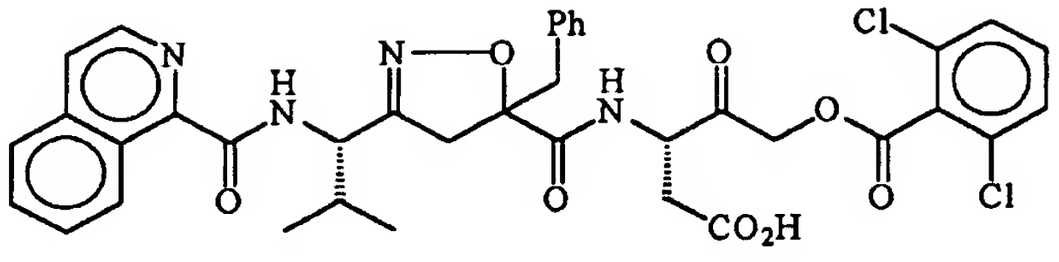
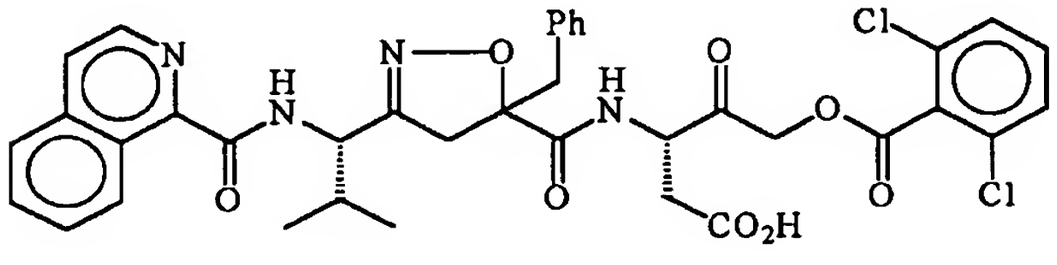
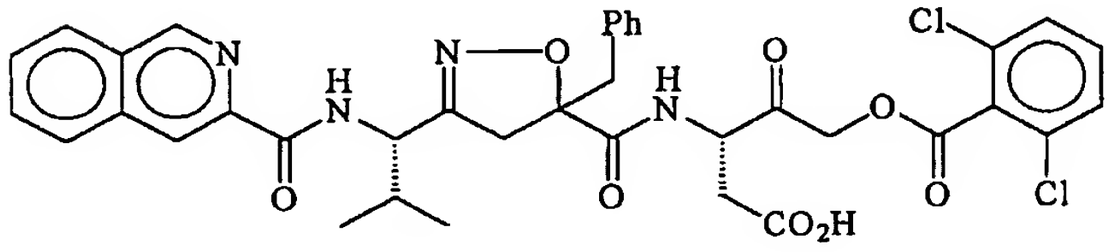
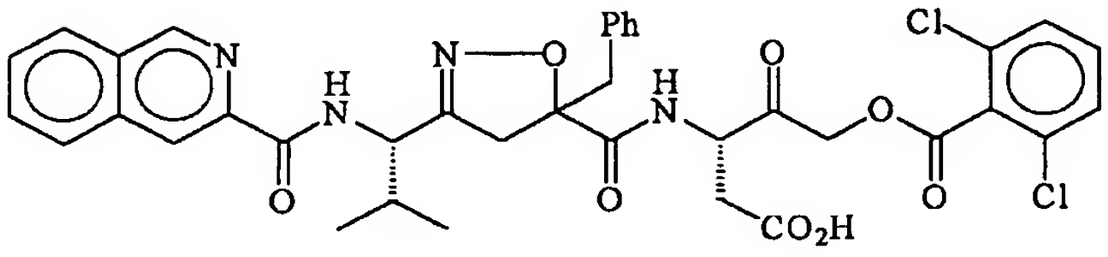
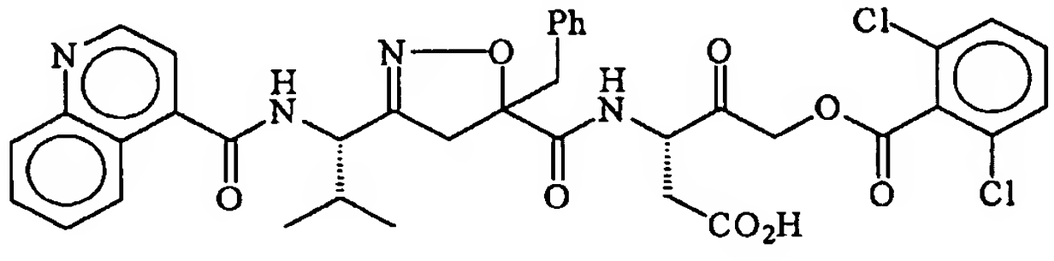


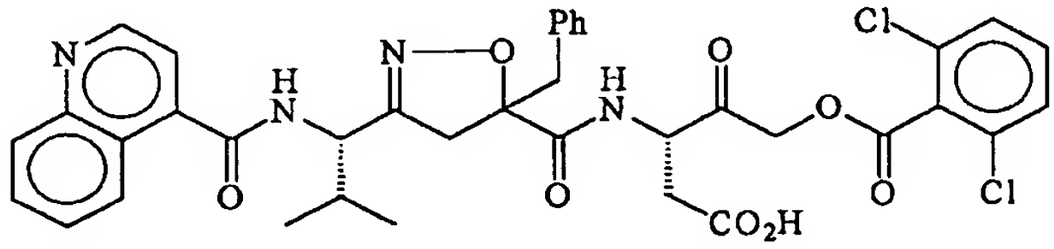
(49)  LP

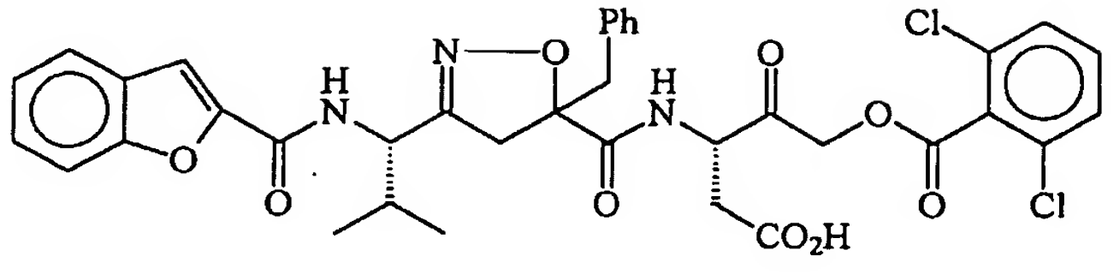
(50)  MP

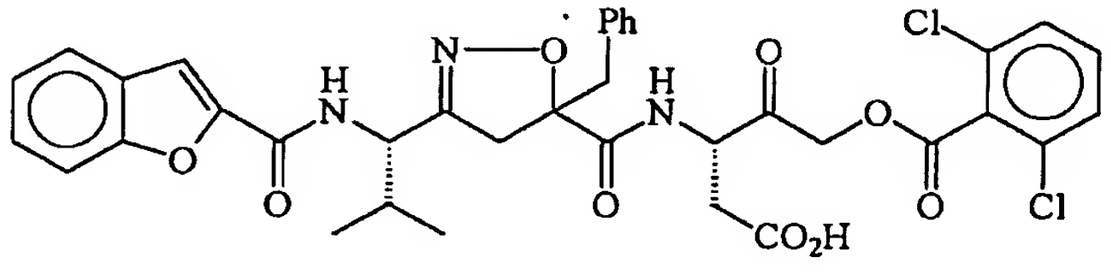
(51)  LP

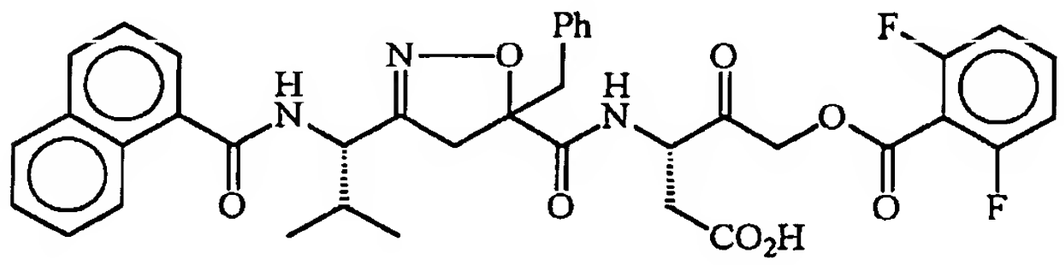
(52)  MP

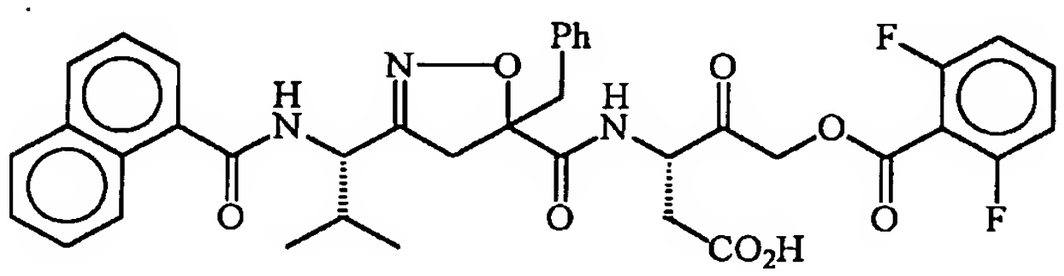
(53)  LP

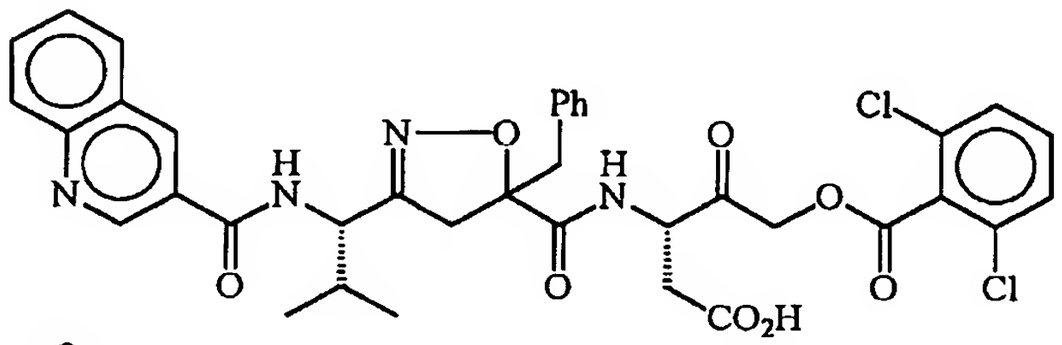
(54)  MP

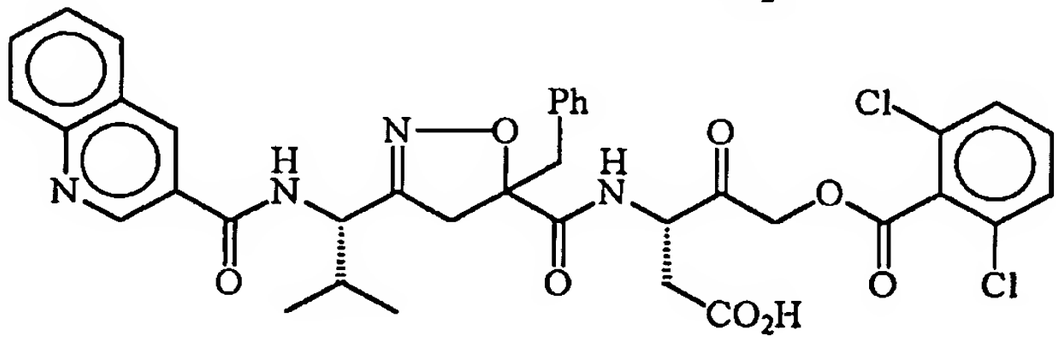
(55)  LP

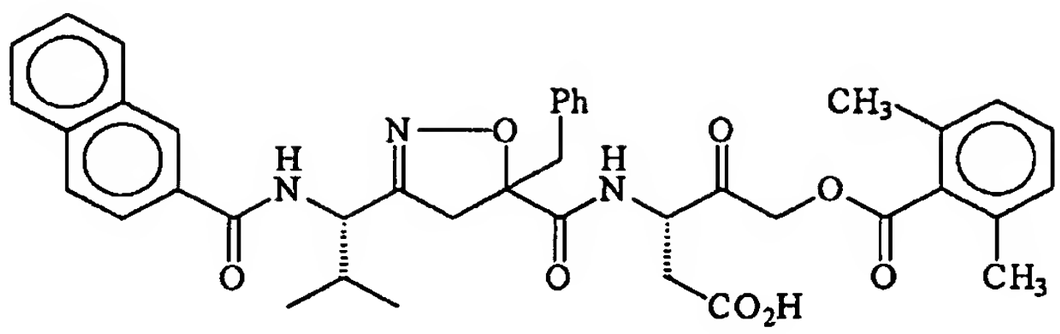
(56)  MP

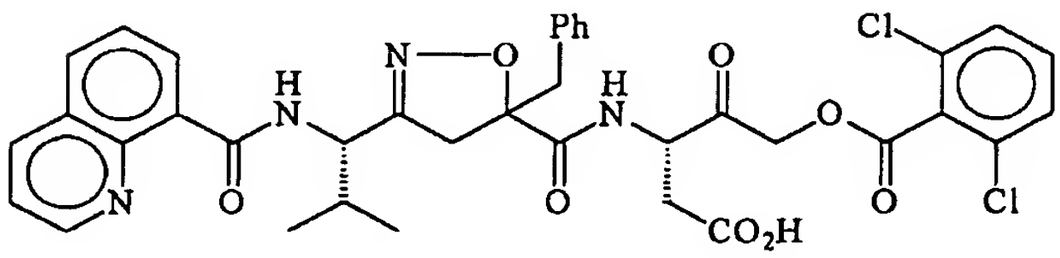
(57)  LP

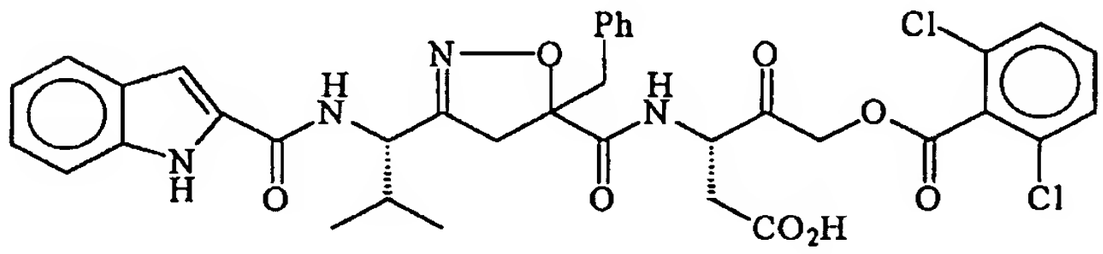
(58)  M

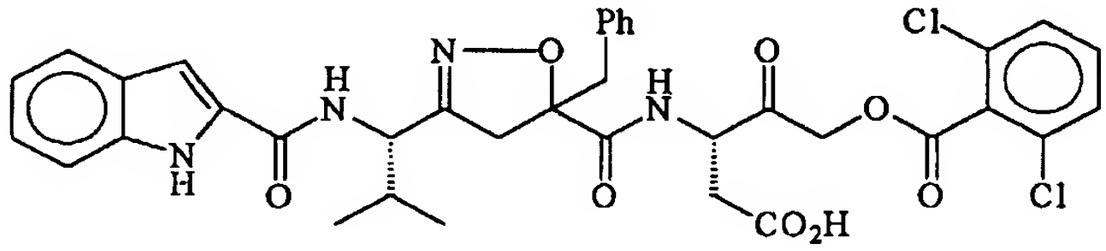
(59)  LP

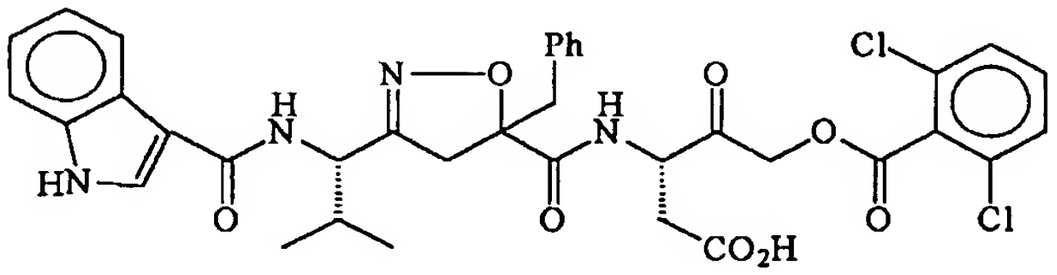
(60)  M

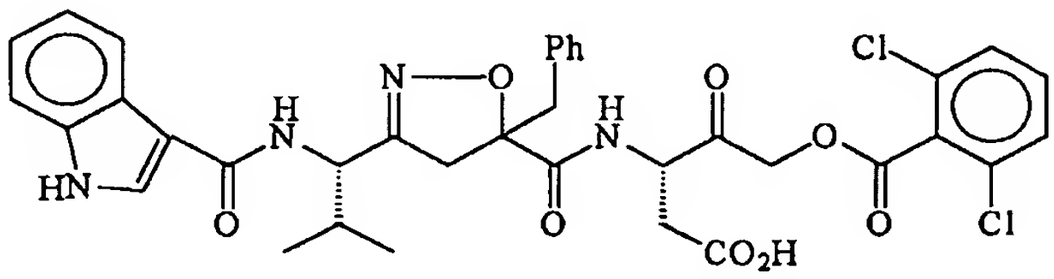
(61)  Mi

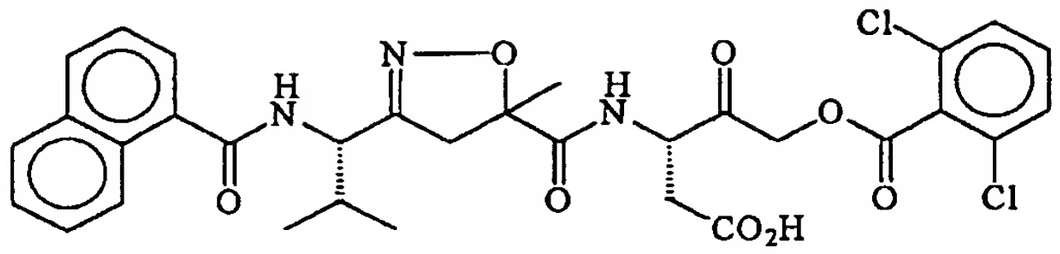
(62)  Mi

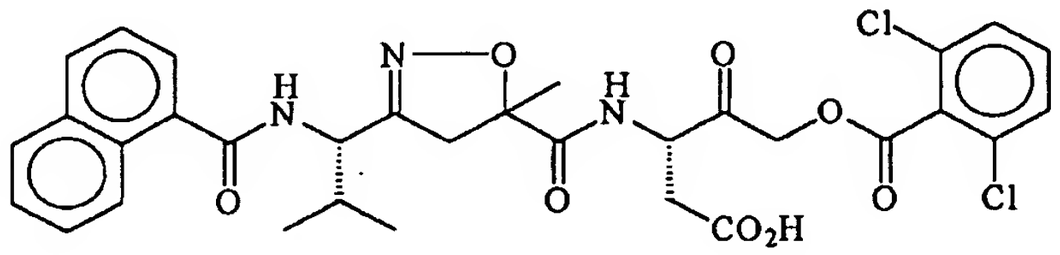
(63)  LP

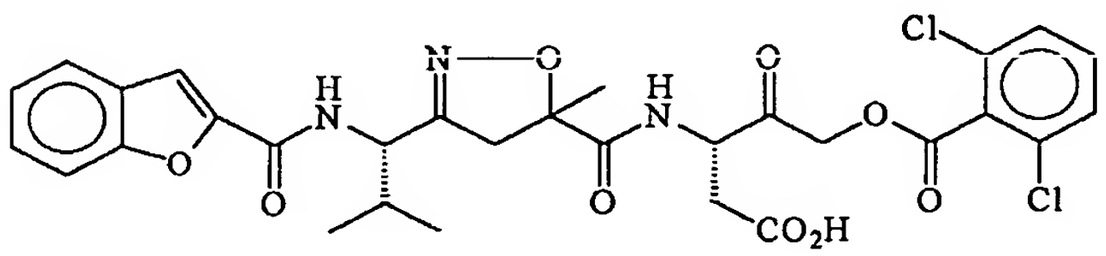
(64)  MP

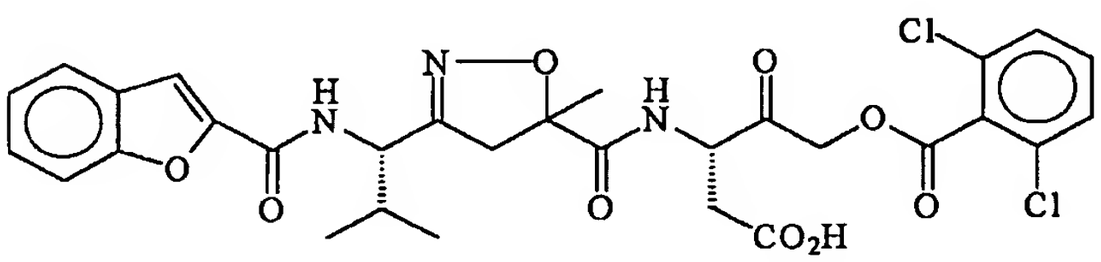
(65)  LP

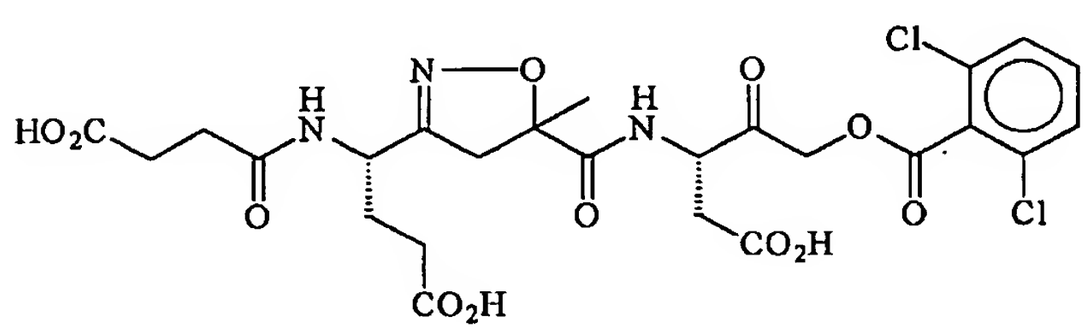
(66)  MP

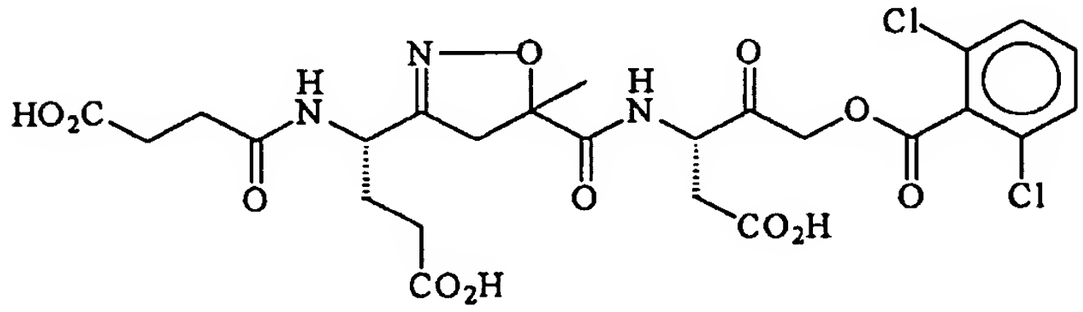
(67)  LP

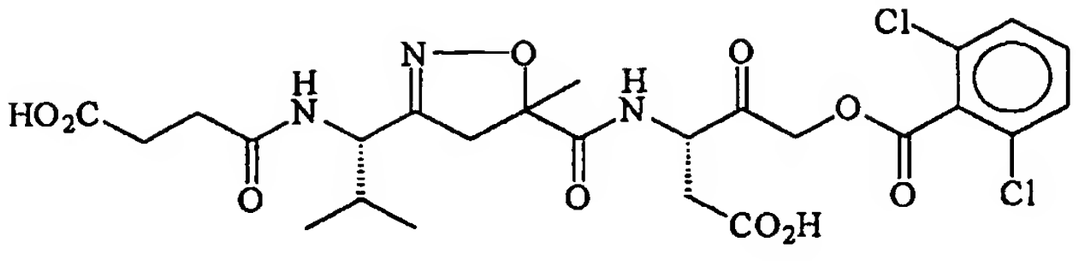
(68)  MP

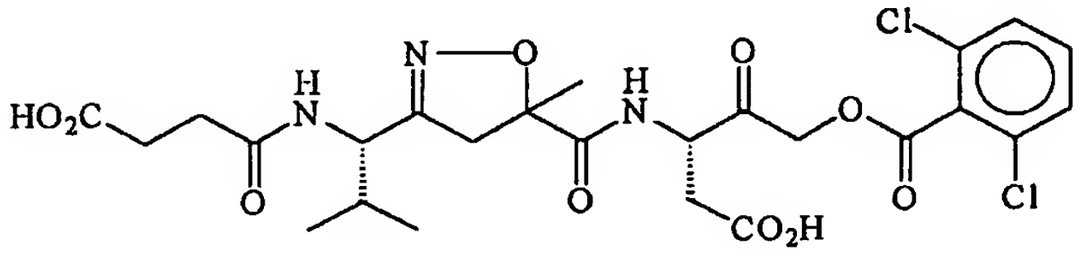
(69)  LP

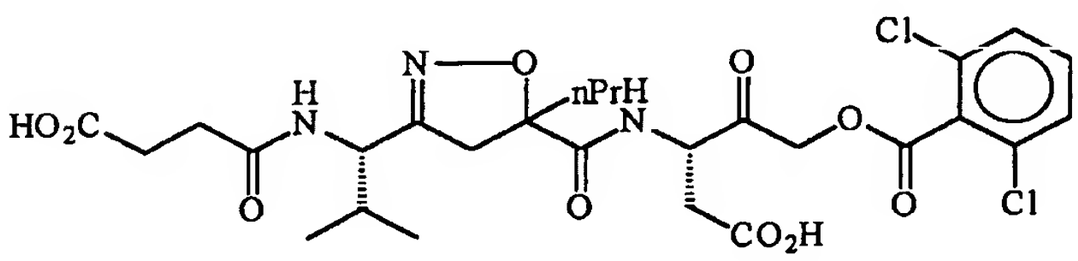
(70)  MP

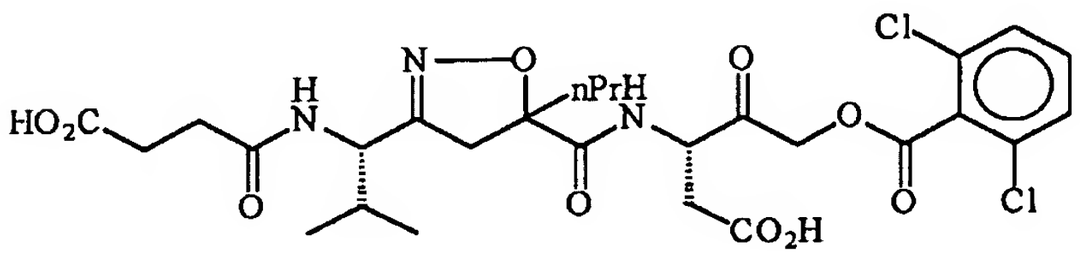
(71)  LP

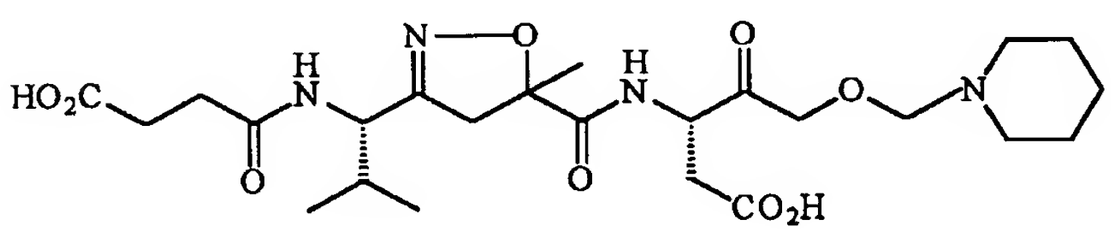
(72)  MP

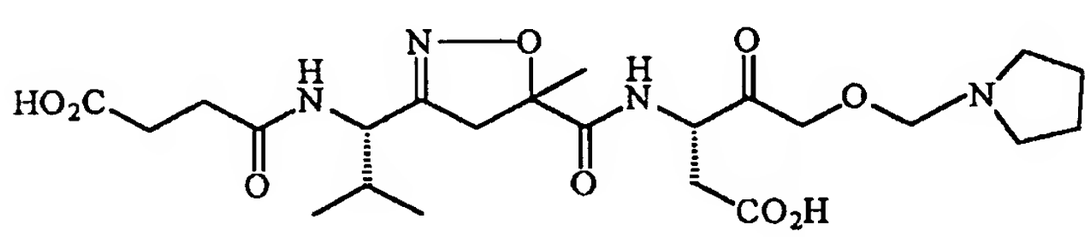
(73)  LP

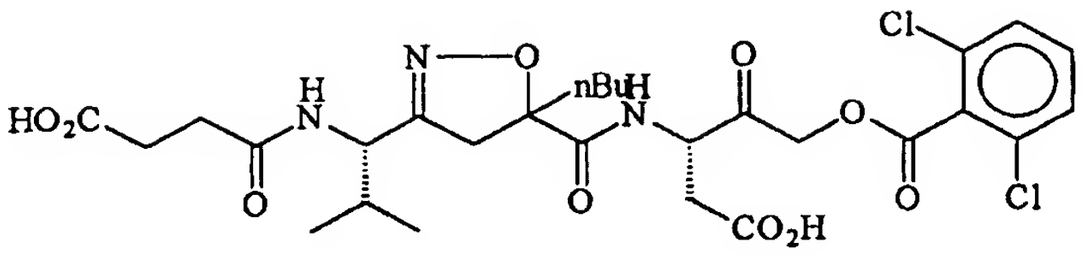
(74)  MP

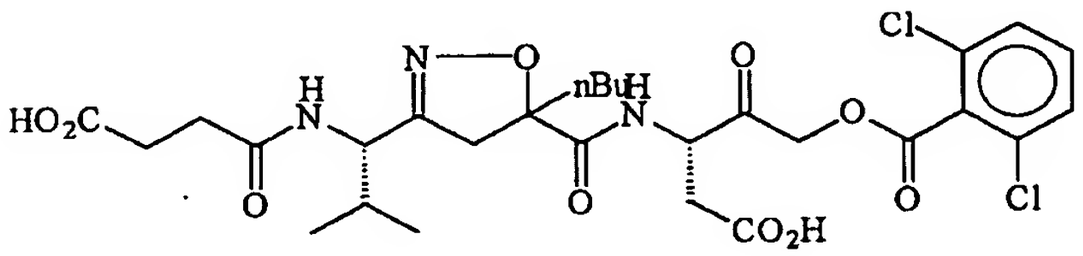
(75)  LP

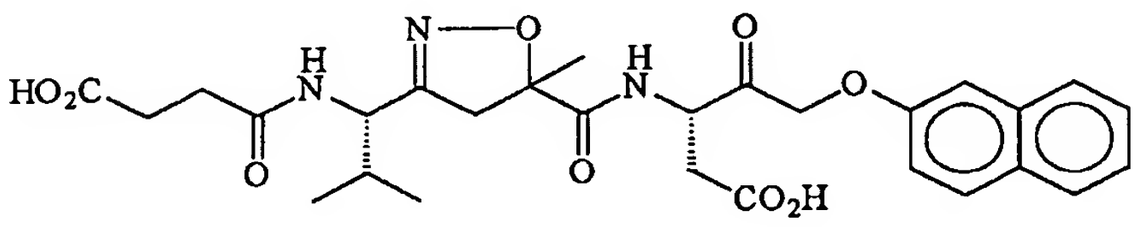
(76)  MP

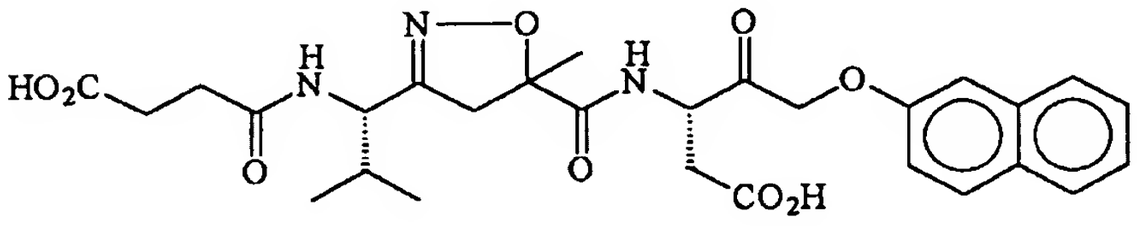
(77)  Mi

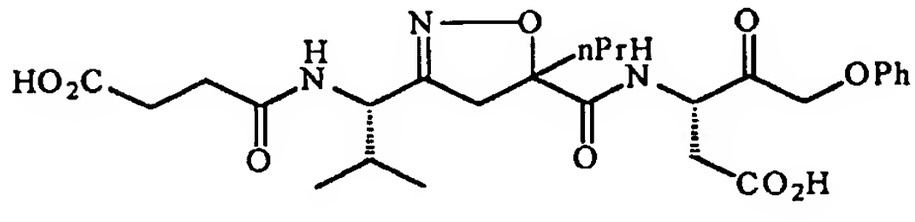
(78)  Mi

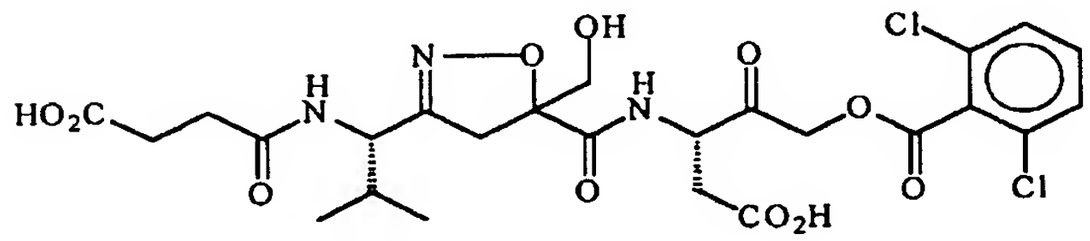
(79)  LP

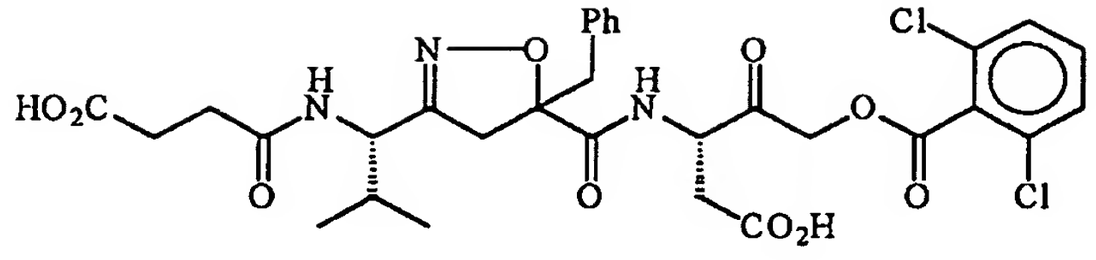
(80)  MP

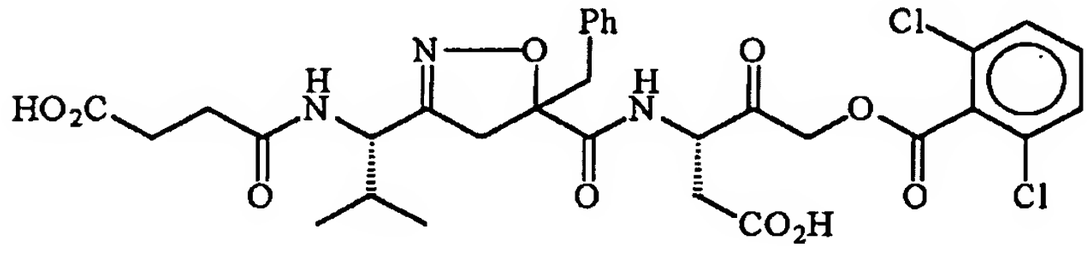
(81)  LP

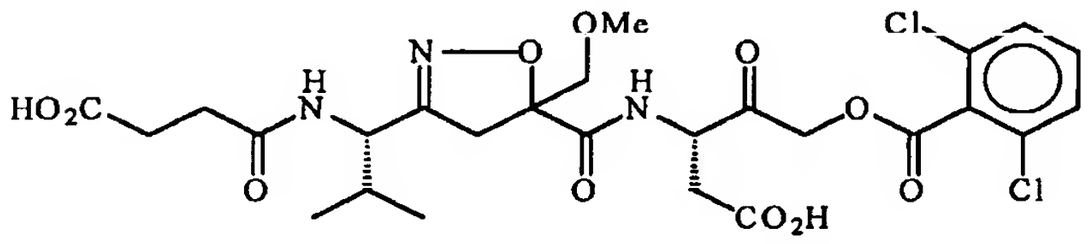
(82)  MP

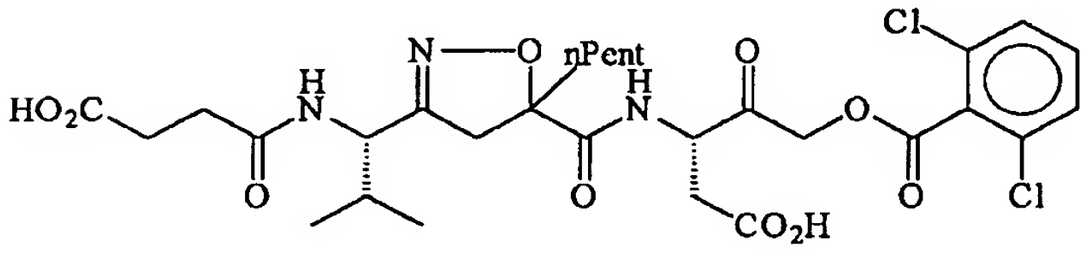
(83)  Mix

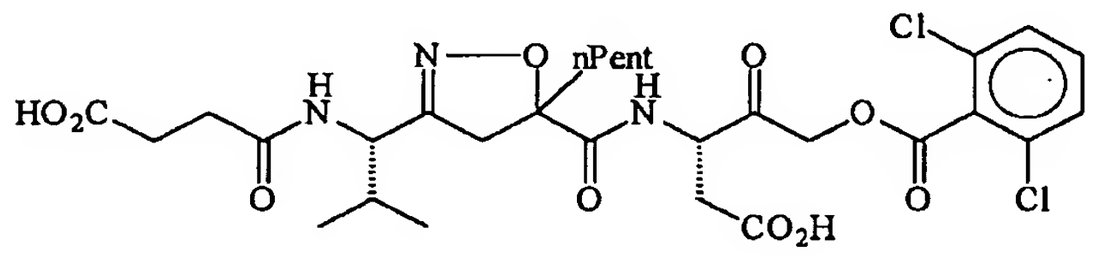
(84)  Mix

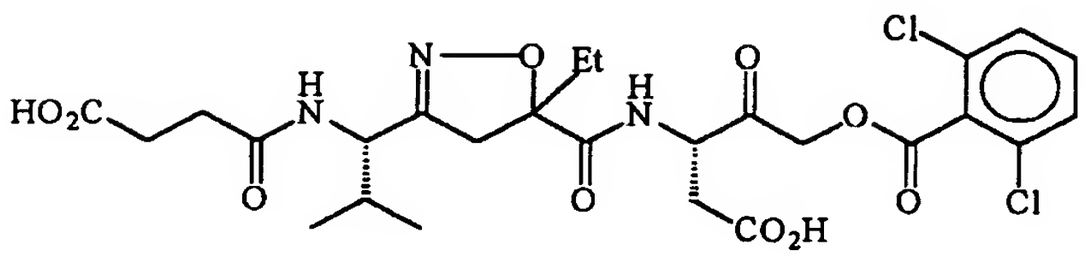
(85)  LP

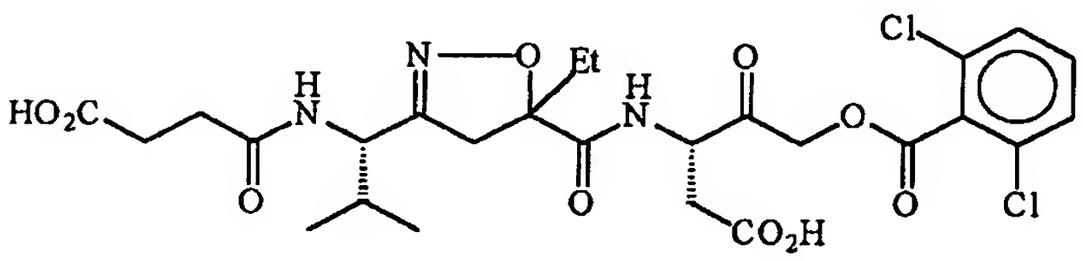
(86)  MP

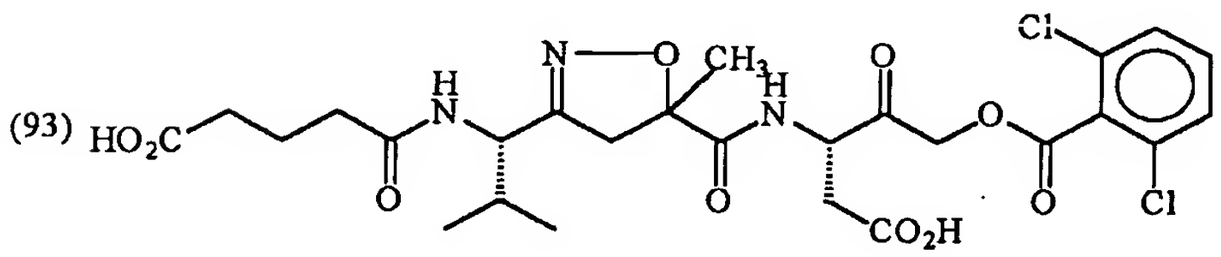
(87)  Mix

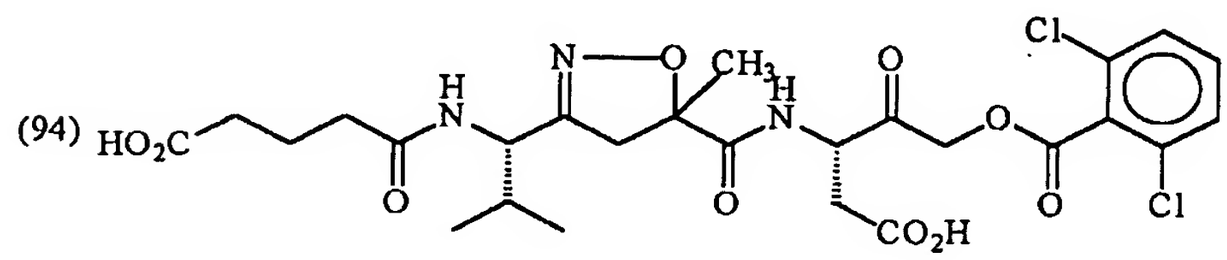
(89)  LP

(90)  MP

(91)  LP

(92)  MP

(93)  LP

(94)  MP

The isoxazoline derivative of formula (I) and the pharmaceutically acceptable salts, esters, and isomers thereof have useful pharmacological properties. For example, they have an inhibitory activity for caspases. Due to their pharmacological activity such as effects on anti-inflammation or inhibition of apoptosis, they can effectively be used as the therapeutics for a number of diseases, for example, the disease in which cells are abnormally died, dementia, cerebral stroke, brain impairment due to AIDS, diabetes, gastric ulcer, cerebral injure by hepatitis, fulminant hepatic failure (FHF), sepsis, organ transplantation rejection reaction, rheumatic arthritis, cardiac cell apoptosis due to ischaemic cardiac diseases and anti-inflammation.

In particular, the composition according to the invention can preferably be used as the therapeutics for fulminant hepatic failure.

As described in detail hereinafter, the present inventors examined, using the compound of formula (I), *in vitro* and *in vivo* caspase inhibitory activities, the viability ratio of hepatocytes in case where hepatic diseases were induced by ConA or TNF_{α} /Actinomycin D, therapeutic effect against hepatitis, reduction of hepatocytic apoptosis, and inhibition of PARP cleavage.

The present inventors have also conducted experiments on the effect of the compound of formula (I) according to the invention on cellular viability in case where apoptosis was induced by IFN_{γ} and anti-Fas antibody, and compared the results thereof with the existing caspase inhibitors, Ac-DEVD-CHO and/or z-DEVD-cmk. Briefly, we examined the efficacy of the new caspase inhibitor of formula (I) to inhibit Con A-induced acute hepatic failure in mice. As a result, this small-molecule, non-peptide-based inhibitor showed inhibition of not only caspase activities but also apoptotic death of hepatocytes *in vitro* and *in vivo*. These results suggest that the compound of formula (I) according to the present invention could be a candidate of therapeutic agent for human FHF caused by massive apoptotic death of hepatocytes.

The compound of the invention is a small-molecule, non-peptide-based caspase inhibitor which has a broad-spectrum activity (see Figures 1 & 2). The compound of formula (I) is different from BCNU or COX-2 inhibitor in the fact that it was originally designed as a specific inhibitor of caspase family enzymes. It is noteworthy that apoptotic process is very

complicated and caspases are critically involved in several steps of this process. Moreover, relatively little is known about caspase regulation largely because many of the known substrates have been found serendipitously. Thus, to block short-term, massive apoptosis of hepatocytes during acute phase of FHF, a broad-spectrum caspase inhibitor might exert more potent effect than a specific-spectrum caspase inhibitor. In this regard, the compound of formula (I) could be an ideal candidate.

The present inventors used ConA-induced hepatitis model to test the apoptosis-blocking effect of caspase inhibitor, the compound of formula (I).

Several cytokines are involved in Con A-induced hepatitis: IL-2, IFN_{γ}, TNF_{α}, IL-6, IL-4, and IL-10. The present inventors assessed the effect of the compound of formula (I) to serum IL-1β, IL-2 IL-4, and IFN_{γ} concentrations elevated by Con A. As a result, the compound of formula (I) according to the present invention significantly suppressed IL-1β level in a dose-dependent manner (see Figure 5A) due to its caspase-1-inhibiting activity shown in Figures 1 and 2. However, the compound of formula (I) did not significantly affect IL-2, IL-4, and IFN_{γ} levels (Figure 5B, C, D). These results could be attributed to the fact that the major cell population to which the compound of formula (I) exerted its activity as a caspase inhibitor is Fas-expressing hepatocytes. The compound of formula (I) rescued hepatocytes from caspase-involved apoptosis, but did not directly suppress activated T cells. One of the biosubstrates for caspase-3-like protease in cells is PARP (116 kDa) which is cleaved into 85- and 31-kDa fragments in cells undergoing apoptosis. Therefore, the appearance of an 85 kDa-cleavage product of PARP has been proposed as an early marker of apoptosis (See, Lazebnik, Y. A. et al., 1994, *Nature* 371: 346-347; Kaufmann, S. H. et al., 1993, *Cancer Res.* 53: 3976-3985).

The compound of formula (I) inhibited PARP cleavage caused by Con A-induced apoptotic death of hepatic cells in a dose-dependent manner (see Figure 7). On Western blot analysis, the amount of 85 kDa-cleavage product gradually reduced as dose of compound 33 is increased, but intact 116 kDa PARP appeared relatively constant. It is considered the hepatocytes which virtually underwent apoptosis comprise only a small portion compared with the whole liver mass. This result is consistent with histological examination. As shown in Figure 6, Con A induced severe morphological and histological changes to hepatocytes and the apoptotic lesions were clearly detectable. However, a large proportion of hepatocytes still remained alive and apoptotic cells comprise a part. This phenomenon explains the appearance of intact 116 kDa PARP even in the liver of ConA/vehicle mice.

Meantime, the present inventors induced an artificial apoptosis by treating Fas responsive cell with IFN_{γ} and anti-Fas antibody, and conducted experiments in order to evaluate the inhibitory activity of the compound of formula (I) on the cells against apoptosis. As a result, the inventors discovered that the compound of formula (I) revealed 2-fold or more superior inhibitory effect over the known Ac-DEVD-CHO or z-DEVD-cmk (At the same concentration, the cell viability was 35.1%(Ac-DEVD-CHO) , 47.3%z-DEVD-cmk, and 100%(Compound 33), see Table 1 and Fig. 8).

From the above experiment results, it is noted that the non-peptidic compound of formula (I) has a wide variety of caspase inhibitory activities and thus, anti-inflammation and apoptosis prevention effects, especially can effectively be used as therapeutics for preventing massive apoptosis of hepatocytes in human FHF.

The compound of formula (I) is a new, non-peptide based caspase inhibitor. Its broad-spectrum activity could be a beneficial property as a therapeutic agent blocking the massive apoptosis of hepatocytes in human FHF.

The compounds of the present invention, therefore, may be used as medicines against above-mentioned diseases. Said use as a medicine or method of treatment comprises local or systemic administration to patients of an effective amount of the compounds according to the invention for treating the diseases.

The subject compounds may be formulated into various pharmaceutical forms for administration purposes. Said pharmaceutical forms or compositions are deemed to novel and consequently constitute a further aspect of the present invention. Also the preparation of said composition constitutes a further aspect of the present invention. To prepare the pharmaceutical composition of this invention, an effective amount of the compound, in base or salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier which may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, percutaneously, or by parenteral injection. It is especially advantageous to formulate the above pharmaceutical composition in unit dosage form for ease of administration and uniformity of dosage. For example, in preparing the composition in oral dosage form, any of the usual pharmaceutical media may be employed for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as

suspensions, syrups, elixirs and solutions: or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agent and the like in the case of powders, pills, capsules and tablets. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. It is preferable that tablets and fills are enteric-coated.

For parenteral compositions, the carrier will usually include sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example sterilized aqueous injection suspension or oil suspension, may be prepared with suitable dispersing agents, wetting agents or suspending agents. Solvents which can be used for this purpose include water, Linger's solution, isotonic NaCl solution, etc. Sterilized fixed oils can also be used as a solvent or a suspending medium. Any non-excitatory fixed oils including mono-, diglycerides can be used for this purpose and fatty acids such as oleic acid can be used in the injectable preparation.

In the preparation suitable for percutaneous administration, the carrier optionally includes a penetration enhancing agents and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, wherein the additives do not give a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may assist preparation of the desired compositions. These compositions may be administered in various routes, e.g., as a transdermal patch, as a spot-on or as an ointment.

Dosage unit as used in the specification and claims herein refers to physically discrete units suitable as unitary dosage, each unit containing a

predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets, capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

In view of the usefulness of the subject compounds in the treatment of the disease in which cells are abnormally died, dementia, cerebral stroke, AIDS, diabetes, gastric ulcer, hepatic injure by hepatitis, sepsis, organ transplantation rejection reaction and anti-inflammation, it is evident that the present invention provides a method of treating patients suffering from the diseases, which comprises the local or systemic administration of a pharmaceutically effective amount of the compound of formula (I) or the pharmaceutically acceptable salt, ester or stereochemically isomeric form thereof in admixture with a pharmaceutical carrier.

Those skilled in the treatment of the diseases associated could easily determine the effective amount of the caspase inhibitor, especially the compound of formula (I) to be administered into a subject. In general, it is contemplated that an effective amount would range from 0.01 mg/kg to 100 mg/kg body weight a day in a unit dosage or divided dosage. However, it is evident to those skilled in the art that such amount ranges are guidelines only and are not intended to limit the scope or use of the invention in any manner. The specific dosage level for a specific subject would depend upon the particular compound to be employed, weight of a subject, health conditions, regimen, administration period of the drug, administration route, excretion rate, combination of drug, the severity of diseases, etc.

The present invention will be described in greater detail through the following examples. The examples are presented for illustrating purposes only and should not be construed as limiting the invention which is properly delineated in the claims.

EXAMPLES

(A) Hydroxamoyl chloride synthesis (Examples 1 to 4)

Example 1: Synthesis of N-t-butoxycarbonyl-(S)-valinal and N-t-butoxy-carbonyl-(S)-valinal oxime

To a solution of dimethyl sulfoxide (11.7 mL, 3.0 eq) in dry CH_2Cl_2 (~200 mL) under N_2 at -60 °C was added slowly oxalyl chloride (5.78 mL, 1.2 eq). After 10 min., a solution of N-t-butoxycarbonyl-(S)-valinol (11.23g, 55.2 mmol) in CH_2Cl_2 (30 mL) was added slowly, and the flask was rinsed with 20 mL of CH_2Cl_2. The resulting white suspension was stirred for 1h at ~ -50 °C. The reaction solution was treated with diisopropylethylamine (28.8 mL, 3.0 eq) and stirred for about 20 min. at -23 °C then diluted with hexanes (400 mL). The mixture was washed with water(150 mL), 1N-$KHSO_4$ solution (x 3, total 1 L), dried with anhydrous Na_2SO_4, filtered and concentrated. The yellowish liquid obtained was used directly in next step without further purification.

The crude valinal in ethanol (60 mL)-water (30 mL) at water bath temperature was treated with hydroxylamine hydrochloride (5.76g, 1.5 eq) and Na_2CO_3 (4.39g, 0.75 eq.). The reaction generated a lot of solid in 1 min., thus diluted with ethanol-water (1:1, 60 mL) and stirred for 1h. The reaction solution was poured into saturated NaCl (100 mL), and then

extracted with ethyl acetate twice (300 mL). Organic extracts were washed with sat'd $NaHCO_3$ (100mL x 2), dried (anh. Na_2SO_4), filtered and concentrated to yield white powder (11.34g, syn, anti mixture of oximes).

Example 2: Synthesis of (2S)-2-(t-butoxycarbonyl)amino-1-chloro-3-methyl-butane-1-one oxime

N-t-butoxy-carbonyl-(S)-valinal oxime (11.34g) in DMF (100 mL) was treated with NCS (7.75g) and stirred in warm water bath (~40 °C) for 1h. After removal of DMF, the residue was extracted with ethyl acetate-hexanes (1:1, 150 mL), washed with water (100 mL x 3), dried (anh. Na_2SO_4), filtered and concentrated to give 13.69g of the title compound.

Example 3: Synthesis of 4-(9-fluorenylmethoxycarbonyl)amino-(4S)-5-hydroxy-pentanoic acid t-butyl ester

To a solution of N-(9-fluorenylmethoxycarbonyl)-γ -t-butyl glutamic acid (8.51g, 20.0 mmol) and NMM (2.42mL, 1.1 eq) in dry THF (110 mL) under N_2 at 0 °C was added isobutyl chloroformate (2.72mL, 1.05eq). After 20 min., the reaction mixture was filter-added to a solution of $NaBH_4$ (1.5g) in THF (120mL)-MeOH (30 mL) at -78 °C under N_2 and rinsed with dry THF (20mL). After stirring for 2.5h at -78 °C, the reaction was quenched with acetic acid (13mL). After concentrating to ~ 50mL, the residue was dissolved in ethyl acetate-hexanes (200 mL,1:1), washed with water (150 mL x 2). Aqueous layer was re-extracted with ethyl acetate-hexanes (150 mL,1:1). Combined extract was washed with sat'd $NaHCO_3$ (150 mL x 2), dried (anhydrous Na_2SO_4), filtered and concentrated to give 8.30g of the title compound as glasslike solid. The

crude alcohol was used directly.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.77 (2H, d, J=7.3Hz), 7.66 (2H, d, J = 7.8 Hz), 7.41 (2H, t, J = 7.3 Hz), 7.31 (2H, pseudo t, J = 7.8, 7.3 Hz), 5.18 (NH, d), 4.41 (2H, m), 4.22 (1H, m), 3.72-3.57 (3H, m), 2.33 (2H, m), 1.93-1.77 (2H, m), 1.45(9H, s).

Example 4: Synthesis of 4-(9-fluorenylmethyloxycarbonyl)amino-(4S)-5-chloro-5- hydroxyimino-pentanoic acid t-butyl ester

To a solution of DMSO (3.0 mL) in dry CH_2Cl_2 (100 mL) at -65°C under N_2 was added oxalyl chloride (2.10 mL, 1.2eq) slowly. After 15 min., a solution of 4-(9-fluorenylmethyloxycarbonyl)amino-(4S)-5-hydroxypentanoic acid t-butyl ester (8.30 g, 20 mmol) in CH_2Cl_2 (50 mL) was added and rinsed with dry CH_2Cl_2 (20 mL). The resulting solution was stirred for 2h at -40 ~ -50 °C. $EtN(i\text{-}Pr)_2$ (10.45 mL, 3.0eq) was added thereto and the reaction solution was slowly warmed up to -10 °C with TLC checking (conversion to aldehyde is relatively slow, ~1h). The reaction mixture was diluted with hexanes (300 mL), washed with water(150 mL), with 1N-$KHSO_4$ (x 3, total 500 mL), dried with anh. Na_2SO_4, filtered and concentrated to give the corresponding aldehyde.

The crude aldehyde in ethanol(60 mL)-CH_2Cl_2 (30 mL)-water(10 mL) at 0°C was treated with $H_2NOH \cdot HCl$ (2.08 g, 1.5eq) and Na_2CO_3 (1.60g, 0.75 eq). The reaction was stirred at room temperature for 30 min., then water (10 mL) was added and stirred for additional 1h. The reaction was stirred further(1h) with additional $H_2NOH \cdot HCl$ (400 mg) and Na_2CO_3 (320 mg). Most of the volatiles were removed in vacuo, and the residue was taken up with ethyl acetate (200 mL), washed with water(100 mL), sat'd $NaHCO_3$ (100 mL), dried (anh. Na_2SO_4), filtered and concentrated to

give the desired oxime (8.30g, syn + anti) as white powder.

The crude oxime in DMF (35 mL) was treated with NCS (2.67g, 20.0 mmol). The reaction was stirred in warm (40°C) bath for 1h. After removal of the DMF in high vacuum rotary evaporator, the residue was taken up with hexane-ethyl acetate (1:1, 150 mL), washed with water (100 mL x 3), dried (anh. Na_2SO_4), filtered and concentrated to give the title compound (9.25g, syn + anti).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.88(1H, s), 7.75(2H, d, J = 7.3Hz), 7.57(2H, m), 7.39(2H, t, J = 7.32Hz), 7.30 (2h, pseudo t, J = 7.8,7.3Hz), 5.46(1H, d), J = 9.3 Hz), 4.63(1H, m), 4.43-4.38(2H, m), 4.19(1H, m), 2.3(2H, m), 2.03(2H, m), 1.43(9H, s). (NMR data reported for major isomer.)

The Following compounds were prepared in the same manner as the above examples.

. 1-chloro-3-methyl-(2S)-2-phenylmethyloxycarbonylamino-butane-1-one oxime,

. 3-(t-butoxycarbonylamino)-(3S)-4- chloro-4-hydroxyimino-butanoic acid methyl ester,

. 3-(phenylmethyloxycarbonylamino)-(3S)-4-chloro-4-hydroxyimino-butanoic acid t-butyl ester, and

. 3-(9-fluorenylmethyloxycarbonylamino)-(3S)-4-chloro-4-hydroxyimino-butanoic acid t-butyl ester.

(B) Synthesis of acrylate derivatives (Examples 5 to 8)

Example 5: Synthesis of ethyl 2-acetoxymethylacrylate

A solution of ethyl 2-hydroxymethyl acrylate (17.3g, 133 mmol, purity ~ 70%, ref: Villieras, J. and Rambaud, M. Synthesis, 1982, *914*) in dry CH_2Cl_2 (200 mL) under N_2 at 0 °C was treated with acetic anhydride (18.8 mL, 1.5 eq) and triethyl amine (37 mL, 2.0 eq). After overnight stirring at room temperature, the reaction was diluted with hexanes (400 mL), washed with sat'd $NaHCO_3$ (300 mL x 2), dried (anh Na_2SO_4), filtered and concentrated. Simple distillation gave 4.6g of the title compound as clear liquid. NMR analysis showed ~ 70 % purity.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.36 (1H, s), 5.84 (1H, s), 4.81(2H, s), 4.25 (2H, q, J = 7.3 Hz), 2.11 (3H, s), 1.31 (3H, t, J = 7.3 Hz)

Example 6: Synthesis of ethyl 2-phenoxymethylacrylate

A solution of ethyl 2-bromomethylacrylate (2.00g, 10.4 mmol, ref: Villieras, J. and Rambaud, M. Synthesis, 1982, *914*) and phenol(975 mg, 1.0eq) in dry THF (20 mL) under N_2 at 0 °C was treated with anhydrous K_2CO_3 (1.43g, 1.0 mol eq). No reaction was observed for 1h. Anhydrous DMF (20 mL) was added and stirred for 2h at 0 °C and for 1h at room temperature. After evaporation of DMF, water(100 mL) was added, and the reaction was extracted with ethyl acetate (100 mL x 2). The organic extract was washed with brine (100 mL), dried (anh. Na_2SO_4), filtered and concentrated. Flash chromatography (40% CH_2Cl_2/hexanes) gave 1.712g (80%) of the title compound.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.30 (2H, yt, J = 7.3 Hz), 6.99-6.96 (3H, m), 6.41 (1H, s), 6.01 (1H, s), 4.78 (2H, s), 4.27 (2H, q, J = 7.33 Hz)

Example 7: Synthesis of ethyl 2-benzylacrylate

To a solution of bromobenzene (7.15g, 45.5 mmol) in THF (30mL) was added n-BuLi (16.6mL, 2.5M in Hexane, 41.4mmol) under N_2 at -78 °C.

It was stirred for 10min. To a suspension of CuCN (3.71g, 41.4mmol) in THF (30mL) was added lithiated benzene solution via cannula under N_2 at -78 °C. The reaction mixture was stirred for another 10 min. at -78 °C and ethyl 2-bromomethyl acrylate (4.00g, 20.7 mmol) in THF was added. The reaction mixture was warmed up to room temperature slowly and quenched with 2N HCl. All precipitates were filtered off and the filtrate was diluted with hexanes (400 mL), washed with sat'd $NaHCO_3$ (300 mL x 2), dried (anh Na_2SO_4), filtered and concentrated. Flash chromatography (2% ethyl acetate-hexanes) gave 3.04g(77%) of the title compounds .
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.34-7.22 (5H, m), 6.26 (1H, s), 5.48(1H, s), 4.22(2H, q, J = 6.3Hz), 3.66 (2H, s), 1.29 (3H, q, J = 6.3 Hz).

Example 8: Synthesis of ethyl 2-(4-bromophenyl)acrylate

The title compound was prepared according to the known procedure (Helvetica Chimica Acta 1986, *69* 2048).
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.46 (2H, d), 7.29 (2H, d), 6.37 (1H, s), 5.90 (1H, s), 4.29 (2H, q), 1.33 (3H, t)

The following compounds were similarly prepared.

· Ethyl 2-(1-naphthyl)acrylate
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.86 (2H, t, J = 7.3 Hz), 7.44 (1H, d, J = 8.8 Hz), 7.48-7.43 (3H, m), 7.37 (1H, d, J = 6.8 Hz), 6.70 (1H, d, J = 2.0 Hz), 5.89 (1H, d, J = 2.0 Hz), 4.22 (2H, q, J = 7.3 Hz), 1.21 (3H, t, J = 7.3 Hz),

· Ethyl 2-(2-naphthyl)acrylate
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.95 (1H, s), 7.90-7.86 (3H, m), 7.59-7.52 (3H, m), 6.47 (1H, d, J = 1.0Hz), 6.06 (1H, d, J = 1.0 Hz), 4.38 (2H, q,

J = 6.8 Hz), 1.40 (3H, t, J = 6.8Hz).

Ethyl 2-butyl acrylate

^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.11 (s, 1H), 5.49 (d, J = 1.4 Hz, 1H), 4.19 (q, J = 6.9 Hz, 2H), 2.29 (m, 2H), 1.45-1.28 (m, 7H), 0.90 (t, J = 7.3 Hz, 3H).

Ethyl 2-propyl acrylate

^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.12 (d, J = 0.9 Hz, 1H), 5.49 (d, J = 1.4 Hz, 1H), 4.20 (q, J = 6.9 Hz, 2H), 2.27 (m, 2H), 1.49 (m, 2H), 1.29 (t, J = 7.3 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H).

Ethyl 2-ethyl acrylate

^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.11 (d, J = 0.9 Hz, 1H), 5.50 (s, 1H), 4.20 (q, J = 6.9 Hz, 2H), 2.32 (m, 2H), 1.29 (t, J = 6.9 Hz, 3H), 1.07 (t, J = 7.4 Hz, 3H).

Ethyl 2-pentyl acrylate

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.12 (s, 1H), 5.50 (s, 1H), 4.21 (q, J = 7.1 Hz, 2H), 2.29 (m, 2H), 1.51-1.13 (m, 9H), 0.89 (t, J = 6.8 Hz, 3H).

(C) General procedure for isoxazoline synthesis (Examples 9 and 10)

Example 9: Synthesis of 3-((1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl)-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester

A solution of (2S)-2-phenylmethyloxycarbonylamino-1-chloro-3-methyl-butane-1-one oxime (640 mg, 2.25mmol) and ethyl 2-phenoxymethylacrylate (464mg) in dry ether(10 mL) under N_2 at -78°C was treated with

triethylamine (627 uL, 2.0 eq). The reaction was stirred overnight, allowing to warm up to room temperature slowly. Water(100 mL) was added, and the reaction was extracted with ethyl acetate (100 mL x 2), washed with water(100mL), dried (anh. Na_2SO_4), filterd and concentrated. Flash chromatography (15% ethyl acetate-hexanes) gave 851mg(83%) of the title compounds as 1:1 mixture of diastereomers.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.34(7H, m), 6.98 (1H, t, J = 7.3Hz), 6.89 (2H, d, J = 7.7Hz), 5.61 (1H, d, J = 9.3 Hz), 5.15-5.08 (2H, m), 4.50 (1H, br s), 4.33-4.22 (4H, m), 3.60-3.54(1H, m), 3.32-3.27(1H, m), 2.10 (1H, m), 1.29 (3H, m), 1.02-0.94 (6H, m).

The following compounds were prepared similarly:

· Ethyl 3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carboxylate (diastereomeric)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.45-7.15 (m, 10H), 5.07 (m, 2.5H), 4.90 (d, 0.5H), 4.30-4.18 (m, 3H), 3.36-2.88 (m, 4H), 1.95-1.80 (m, 1H), 1.27 (m, 3H), 0.86-0.55 (m, 6H).

· 3-[(1S)-1-t-butoxycarbonylamino-2-methyl-propyl]-5-(2-naphthyl)-4,5-di-hydro-isoxazole-5-carboxylic acid ethyl ester

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.97(1H, s), 7.86-7.82 (3H, m), 7.52-7.48 (3H, m), 4.93 (1H, br), 4.37 (1H, m), 4.25 -4.18 (2H, m), 4.10-4.05 (1H, two doublets, J=17.1, 17.6 Hz), 3.28-3.22 (1H, two doublets, J = 17.1, 17.1 Hz), 2.05 (1H, m), 1.43 ((H, s), 1.24-1.20 (3H, m), 0.98-0.91 (6H, m).

· 3-[(1S)-1-t-butoxycarbonylamino-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (~1:1 diastereomers)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.25 (5H, m), 4.82 and 4.60 (1H, two m), 4.25-4.15 (3H, m), 3.38-3.29 (2H, m), 3.10 (1H, m), 2.90 (1H, m), 1.43 and 1.42 (9H, two s), 1.27 (3H, m), 0.90-0.80 (6H, m).

· 5-acetoxymethyl-3-[(1S)-1-t-butoxy-carbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester

^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.93 (1H, br), 4.44-4.26 (5H, m), 3.50 (1H, m), 3.10 (1H, m), 2.08 (4H, s + br 1H), 1.46 (9H, s), 1.32-1.30 (3H, m), 1.02-0.96 (6H, m).

· Ethyl 3-[2-methyl-(1S)-1-(tert-butyloxycarbonylamino)-propyl]-5-butyl-4,5-dihydro-isoxazole-5-carboxylate (diastereomeric mixture)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.96 & 4.87 (two br s, 1H), 4.34-4.18 (m, 3H), 3.42-3.36 (m, 1H), 2.90-2.83 (m, 1H), 2.02 (m, 1H), 1.91 (m, 2H), 1.43 (s, 9H), 1.37-1.26 (m, 7H), 0.98-0.87 (m, 9H).

· Ethyl 3-[2-methyl-(1S)-1-(tert-butyloxycarbonylamino)-propyl]-5-propyl-4,5-dihydro-isoxazole-5-carboxylate (diastereomeric mixture)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.96-4.86 (m, 1H), 4.33-4.18 (m, 3H), 3.42-3.36 (m, 1H), 2.90-2.83 (m, 1H), 2.02 (m, 1H), 1.89 (m, 2H), 1.43 (s, 9H), 1.29 (m, 5H), 0.98-0.87 (m, 9H).

· Methyl 3-[2-methyl-(1S)-1-(tert-butyloxycarbonylamino)-propyl]-5-methoxy-methyl-4,5-dihydro-isoxazole-5-carboxylate (diastereomeric mixture)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.92 (m, 1H), 4.35 (m, 1H), 3.80 & 3.79 (two s, 3H), 3.40 (s, 3H), 3.88-3.13 (m, 4H), 2.04 (m, 1H), 1.44 (s, 9H), 0.99-0.91 (m, 6H).

· Ethyl 3-[2-methyl-(1S)-1-(tert-butyloxycarbonylamino)-propyl]-5-n-pentyl-4,5-dihydro-isoxazole-5-carboxylate (diastereomeric mixture)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.95& 4.88 (two br s, 1H), 4.30-4.17 (m, 3H), 3.42-3.36 (m, 1H), 2.89-2.83 (m, 1H), 2.02 (m, 1H), 1.90 (m, 2H), 1.43 (s, 9H), 1.28 (m, 9H), 0.98-0.85 (m, 9H).

· Ethyl 3-[2-methyl-(1S)-1-(tert-butyloxycarbonylamino)-propyl]-5-ethyl-4,5-dihydro-isoxazole-5-carboxylate (diastereomeric mixture)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.96& 4.88 (two br s, 1H), 4.31-4.18 (m, 3H), 3.42-3.36 (m, 1H), 2.89-2.80 (m, 1H), 2.03 (m, 1H), 1.94 (m, 2H), 1.43 (s, 9H), 1.29 (m, 3H), 0.97-0.86 (m, 9H).

Example 10: Synthesis of 3-[(1S)-1-(9-fluorenylmethyloxycarbonylamino)-3-t-butoxycarbonyl-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester

A solution of 4-(9-fluorenylmethoxycarbonyl)amino-(4S)-5-chloro-5-hydroxy-imino-pentanoic acid t-butyl ester (3.44g, 7.50 mmol) and methyl methacrylate (2.40mL, 3.0 eq) in dry ether under N_2 at -78 °C was treated with $EtN(i\text{-}Pr)_2$ (1.96mL, 1.5eq). Similar treatment as described previously followed by flash chromatography with 25-30% ethyl acetate/hexanes gave 3.46g (89% overall) of the title compound as diastereomeric mixture.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.77 (2H, d, J=7.3Hz), 7.59 (2H, d, J =7.3Hz), 7.40 (2H, t, J = 7.3Hz), 7.31 (2H, t, J =7.3 Hz), 5.34 (1H, m), 4.58-4.38 (3H, m), 4.21 (1H, m), 3.78 (3H, s), 3.48 (1H, m), 2.90-2.81 (1H, m), 2.42-2.27 (2H, m), 2.18 (1H, m), 1.93 (1H, m), 1.63 (3H, s),

1.45 (9H, s)

(D) Transformations of isoxazolines (Deprotection, Introduction of P_4 group, Hydrolysis of ester group) (Examples 11 and 12)

Example 11: Synthesis of 3-{2-methyl-(1S)-1-(naphthalene-2-carbonyl-amino)-propyl}-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester

A solution of 3-{(1S)-1-(t-butoxycarbonylamino)-2-methyl-propyl}-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (2.00g, 4.76 mmol) in dry CH_2Cl_2 (10 mL) at 0°C under N_2 was treated with TFA (6 mL) and stirred for 1.5h. After removal of volatiles, the residue was taken up with ethyl acetate (200 mL), washed with sat'd $NaHCO_3$ (100 mL x 2), dried (anh Na_2SO_4), filtered and concentrated. To a solution of the crude product, EDC (1.09g, 1.2 eq), 2-naphthoic acid (983 mg, 1.2 eq) and HOBt (771 mg, 1.2 eq) in DMF (20 mL) at 0°C was added triethylamine (663 uL, 1.0 eq). The reaction was stirred overnight at room temperature. After removal of volatiles in vacuo, the residue was taken up with ethyl acetate (250 mL), washed with water(100 mL), sat'd $NaHCO_3$ (100 mL x 2), dried (anh Na_2SO_4), filtered and concentrated. Flash chromatography with 25-33% ethyl acetate/hexanes gave 2.04g (90%) of the title compound.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.30 (1H,s), 7.93-7.84 (4H, m), 7.58-7.52 (2H, m), 7.29-7.22 (2H, m), 7.00-6.81 (4H, m), 5.06-5.01 (1H, m), 4.36-4.24 (4H, m), 3.68-3.61 (1H, m), 3.43-3.39 (1H, m), 2.28 (1H, m), 1.31-1.26 (3H, m), 1.12-1.05 (6H, m).

Hydrolysis of isoxazoline 5-carboxylic acid ester: The above compound

(2.04g) in distilled THF (40 mL) (not completely soluble) was treated with 1N-NaOH(5.2 mL, 1.2 eq). After 4h (~50% completion), additional 1N-NaOH (1.0 mL) was added. After stirring overnight, the reaction was neutralized with concentrated 1N-HCl. The residue was taken up with CH_2Cl_2 (>700 mL), washed with water, dried (anh Na_2SO_4), filtered and concentrated to give 1.948g (103%) of the free carboxylic acid, which was used directly in next step.

The following compounds were prepared similarly:

. 3-{2-methyl-(1S)-1-(naphthalene-1-carbonylamino)-propyl}-5-phenoxymethyl -4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.23 (1H, d, J = 8.3 Hz), 7.93-7.86 (2H, m), 7.66 (1H, m), 7.54-7.42 (3H, m), 7.29-7.25 (2H, m), 7.00-6.90 (3H, m), 6.49 (1H, m), 5.13-5.09 (1H, m), 4.40-4.26 (4H, m), 3.69-3.64 (1H, m), 3.44-3.41 (1H, m), 2.28 (1H, m), 1.32-1.01 (9H, m).

. 3-{2-methyl-(1S)-1-(naphthalene-2-carbonylamino)-propyl}-4,5-dihydro-isoxa zole-5-carboxylic acid ethyl ester

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.30 (1H, s), 7.94-7.83 (4H, m), 7.59-7.53 (2H, m), 6.80-6.70 (NH, two d), 5.07-5.03 (2H, m), 4.28-4.21 (2H, m), 3.37-3.33 (2H, m), 2.28 (1H, m), 1.34-1.25 (3H, m), 1.12-1.02 (6H, m).

. 3-[(1S)-1-(1-naphthalenecarbonylamino)-2-methyl-propyl]-5-phenylmethyl-4, 5- dihydro-isoxazole-5-carboxylic acid ethyl ester (diastereomeric)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.28 (d, J = 7.8 Hz, 1H), 7.94-7.86 (m, 2H), 7.61-7.11 (m, 9H), 6.36 (d, J = 9.3 Hz, 0.5H), 6.09 9d, J = 9.3 Hz, 0.5H), 4.94-4.85 (m, 1H), 4.27-4.21 (m, 2H), 3.49-2.98 (m, 4H), 2.15 &

1.97 (two m, 1H), 1.30-1.26 (m, 3H), 1.03-0.59 (m, 6H).

· Ethyl 3-[(1S)-1-phenethylcarbonylamino-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carboxylate (diastereomeric)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.28-7.17 (m, 10H), 5.74 & 5.50 (two d, J = 9.3 Hz, NH), 4.58-4.52 (m, 1H), 4.24-4.20 (m, 2H), 3.34-3.25 (m, 2H), 3.11-2.82 (m, 4H), 2.52-2.45 (m, 2H), 1.93 &1.75 (two m, 1H), 1.29-1.25 (m, 3H), 0.79-0.41 (m, 6H).

· 3-[(1S)-1-(1-naphthalenesulfonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (diastereomeric)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.68-8.64 (m, 1H), 8.29-8.25 (m, 1H), 8.07 (m, 1H), 7.93 (m, 1H), 7.71-7.52 (m, 3H), 7.23-6.98 (m, 5H), 5.27 & 5.19 (two m, 1H), 4.12-4.07 (m, 2H), 3.75 & 3.66 (two m, 1H), 3.16-2.43 (m, 4H), 1.77-1.62 (m, 1H), 1.25-1.16 (m, 3H), 0.86-0.57 (m, 6H).

· 3-[(1S)-1-(indole-3-yl-ethylcarbonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5 -dihydro-isoxazole-5-carboxylic acid ethyl ester (diastereomeric)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.16-8.12 (m, 1H), 7.62-7.56 (m, 1H), 7.36-6.94 (m, 9H), 5.71 (d, J = 9.3 Hz, 0.5H), 5.42 (d, J = 8.8 Hz, 0.5H), 4.56-4.50 (m, 1H), 4.25-4.17 (m, 2H), 3.30-2.51 (m, 8H), 1.89-1.70 (m, 1H), 1.28-1.24 (m, 3H), 0.73-0.41 (m, 6H).

· 3-[(1S)-1-(indole-3-yl-methylcarbonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5 -dihydro-isoxazole-5-carboxylic acid ethyl ester (diastereomeric)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.56 & 8.52 (two br s, 1H), 7.55-7.05 (m, 10H), 5.98-5.91 (m, 1H), 4.57 (m, 1H), 4.22-4.15 (m, 2H), 3.73 (m, 2H), 3.28-2.79 (m, 4H), 1.87-1.68 (m, 1H), 1.27-1.20 (m, 3H), 0.75-0.34

(m, 6H).

· 3-[(1S)-1-(cinnamoylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (diastereomeric)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.61-7.23 (m, 11H), 6.40-6.34 (m, 1H), 6.06 (d, J = 8.8 Hz, 0.5H), 5.81 (d, J = 9.3 Hz, 0.5H), 4.76-4.69 (m, 1H), 4.26-4.19 (m, 2H), 3.42-2.94 (m, 4H), 2.06 & 1.88 (two m, 1H), 1.28-1.24 (m, 3H), 0.93-0.57 (m, 6H).

· 3-[(1S)-1-(phenylmethylsufonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (diastereomeric)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.35-7.16 (m, 10H), 4.66-4.61 (m, 1H), 4.25 (m, 2H), 4.11-3.84 (m, 3H), 3.71-2.82 (m, 4H), 1.80 & 1.70 (two m, 1H), 1.28 (m, 3H), 0.85-0.58 (m, 6H).

· Methyl 3-[2-methyl-(1S)-1-(4-tert-butyloxycarbonylbutanoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylate (diastereomeric mixture)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.05-5.99 (two d, 1H), 4.71 (m, 1H), 3.77 (s, 3H), 3.49-3.44 (m, 1H), 2.87-2.80 (m, 1H), 2.27 (m, 4H), 2.07 (m, 1H), 1.92 (m, 2H), ~1.6 (s, 3H), 1.43 (s, 9H), 1.29 (m, 3H), 0.99-0.86 (m, 6H).

· Ethyl 3-[2-methyl-(1S)-1-(3-tert-butyloxycarbonylproanoylamino)-propyl]-5-ethyl-4,5-dihydro-isoxazole-5-carboxylate (diastereomeric mixture)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.20-6.15 (two d, 1H), 4.68 (m, 1H), 4.21 (m, 2H), 3.40-3.36 (m, 1H), 2.90-2.82 (m, 1H), 2.57 (m, 2H), 2.46 (m, 2H), 2.07 (m, 1H), 1.94 (m, 2H), 1.43 (s, 9H), 1.29 (m, 3H), 0.96-0.88 (m, 9H).

· Ethyl 3-[2-methyl-(1S)-1-(3-tert-butyloxycarbonylproanoylamino)-propyl]-5-n-pentyl-4,5-dihydro-isoxazole-5-carboxylate (diastereomeric mixture)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.18-6.13 (two d, 1H), 4.68 (m, 1H), 4.23 (m, 2H), 3.41-3.36 (m, 1H), 2.90-2.82 (m, 1H), 2.57 (m, 2H), 2.46 (m, 2H), 2.08 (m, 1H), 1.88 (m, 2H), 1.43 (s, 9H), 1.28 (m, 9H), 0.96-0.85 (m, 9H).

· Methyl 3-[2-methyl-(1S)-1-(3-tert-butyloxycarbonylproanoylamino)-propyl]-5-methoxymethyl-4,5-dihydro-isoxazole-5-carboxylate (diastereomeric mixture)
^{i}H-NMR (500 MHz, $CDCl_3$) δ 6.17 (m, 1H), 4.71 (m, 1H), 3.78 (s, 3H), 3.72-3,65 (m, 2H), 3.39 (two s, 3H), 3.39-3.34 (m, 1H), 3.17-3.12 (m, 1H), 2.57 (m, 2H), 2.46 (m, 2H), 2.08 (m, 1H), 1.43 (s, 9H), 0.97-0.88 (m, 6H).

· 3-[2-methyl-(1S)-1-amino-propyl]-5-(2-naphthyl)-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (~1.3:1 diastereomers)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.99 (1H, s), 7.86-7.82 (3H, m), 7.53-7.49 (3H, m), 4.25-4.02 (3H, m), 3.55-3.48 (1H, two d, J = 7.3, 6.8Hz), 3.35 (0.45H, d, J=17.1 Hz), 3.19 (0.55H, d, J = 17.1Hz), 1.78 (1H, m), 1.22 (3H, t, J = 7.3 Hz), 0.96-0.82 (6H, m)

Example 12: Synthesis of 3-{(1S)-1- (2-naphthoylamino)-3-t-butoxycarbonyl-propyl}-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester

A solution of 3-[(1S)-1-(9-fluorenylmethyloxycarbonylamino)-3-t-butoxy-carbonyl-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester (440mg, 0.842 mmol) in DMF (8.0 mL) at room temperature was treated with piperidine (2.5 mL) for 5 min. After concentration, the residue

was dissolved in DMF (10 mL), and treated with 2-naphthoic acid (174 mg, 1.2 eq), EDC (210 mg, 1.3 eq), HOBt (148 mg, 1.3 eq) and triethylamine (0.35 mL, 3.0 eq), then stirred overnight (0°C toroom temperature). Usual workup followed by chromatography gave 133 mg of the title compound and 260 mg (~50% purity) mixture.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.33 (1H, s), 7.92-7.83 (4H, m), 7.58-7.48 (2H, m), 7.34 (1H, d, J=7.8Hz), 5.04 (1H, m), 3.78 and 3.74 (3H, two s), 3.62-3.53 (1H, two d, J=17.1, 17.6Hz), 3.00-2.96 (1H, two d, J =17.1, 17.6 Hz), 2.56-2.08 (4H, m), 1.63 and 1,59 (3H, two s), 1.41 and 1.40 (9H, two s)

(E) Synthesis of aspartic acid derivatives (Examples 13 to 18)

Example 13: Synthesis of N-phenylmethyloxycarbonyl-β -t-butyl aspartic acid (N-methoxy) methyl amide

A solution of N-benzyloxycarbonyl-β -t-butyl aspartic acid (2.0g, 6.2 mmol), N,O-dimethylhydroxylamine hydrochloride (724 mg, 1.2 eq) and HOBt (1.00g, 1.2 eq) in DMF (20 mL) at 0°C was treated with EDC (1.42g, 1.2 eq) and triethylamine (1.29 mL, 1.5 eq). After stirring overnight (0°C toroom temperature), the reaction was diluted with water(100mL), extracted with ethyl acetate-hexanes (1:1, 100 mL x 2), washed with water(100 mL), dried (anh Na_2SO_4), filtered and concentrated. Flash chromatography with ethyl acetate-hexanes (3:7) gave 2.039g (90%) of the title compound.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.36-7.31 (5H, m), 5.70 (1H, br), 5.16-5.08 (3H, m), 3.80 (3H, s), 3.23 (3H, s), 2.74-2.71(1H, m), 2.59 -2.57 (1H, m), 1.43 (9H, s).

Example 14: Synthesis of β -t-butyl aspartic acid N,O-dimethylhydroxyl-amine amide

Conventional hydrogenolysis of N-phenylmethyloxycarbonyl-β -t-butyl aspartic acid (N-methoxy)methyl amide (H_2 balloon, 10% Pd/C, EtOH) gave the title compound (100%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.13 (1H, m), 3.77 (3H, s), 3.22 (3H, s), 2.71-2.67 (1H, m), 2.42-2.38 (1H, m), 1.46 (9H, s)

Example 15: Synthesis of N-phenylmethyloxycarbonyl-β -t-butyl aspartic acid methyl ester

Treatment of N-benzyloxycarbonyl-β -t-butyl aspartic acid with diazomethane/ ether gave the desired methyl ester (100%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.35-7.27 (5H, m), 5.75 (1H, d), 5.13 (2H, s), 4.60 (1H, m), 3.75 (3H, m), 2.90 (1H, m), 2.76 (1H, m), 1.42 (9H, s).

Example 16: Synthesis of β -t-butyl aspartic acid methyl ester hydrochloride

Conventional hydrogenolysis of N-phenylmethyloxycarbonyl-β -t-butyl aspartic acid methyl ester (H_2 balloon, 10% Pd/C, EtOH-HCl) gave the desired product as hydrochloride salt.

Example 17: Synthesis of (3S)-3-phenylmethyloxycarbonylamino-4-hydroxy-5-phenoxy-pentanoic acid t-butyl ester
A solution of N-phenylmethyloxycarbonyl-β -t-butyl-aspartic acid (5.03g,

15.6 mmol), NMM (1.90 mL, 17.1 mmol) in dry THF (60 mL) under N_2 at -15°C was treated with isobutyl chloroformate (2.12 mL, 16.3 mmol) and the resulting suspension was stirred for 20 min. To the mixture at 0°C was added dry diazomethane/ether (synthesized from 2.0 eq of 1-methyl-3-nitro-1- nitroso-guanidine, 60 mL) and stirred for 30 min. When the diazo ketone synthesis was completed (TLC analysis), 30% HBr/AcOH (6.42 mL, 2.0 eq) was introduced thereto (stirred for 30-60 min.) at 0°C. The reaction was extracted with ethyl acetate, washed with sat'd $NaHCO_3$ (x 2), brine, dried (anh. Na_2SO_4), filtered and concentrated to give bromomethyl ketone derivative (6.4g).

The bromomethyl ketone(4.36g) and phenol (1.13g, 1.1 eq) in DMF (18 mL) at room temperature were treated with freshly dried KF (1.58g, 2.5 eq) and stirred for 2 h. Usual extractive workup gave crude phenoxy ketone. The crude phenoxy ketone in methanol (20 mL) at -78 °C was treated with $NaBH_4$ (412 mg) in MeOH (40 mL) (78 °C to room temperature, 2h). The reaction was quenched with acetic acid. Usual extractive workup followed by flash chromatography (ethyl acetate-hexanes = 1:5) gave 2.58g (57%) of the title compound as diastereomeric mixture. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.36-7.26 (7H, m), 6.98-6.87 (3H, m), 5.71-5.53 (NH, two d), 5.10 (2H, s), 4.24-3.92 (4H, m), 2.70-2.63 (2H, m), 1.44 and 1.43 (9H, two s).

The following compound was prepared similarly:

. (3S)-3-phenylmethyloxycarbonylamino-4-hydroxy-5-(1-naphthyl)oxy-pentanoic acid t-butyl ester

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.21 (1H, m), 7.80 (1H, m), 7.50-7.33 (9H, m), 6.80 (1H, m), 5.73 and 5.55 (1H, two d, J = 8.3 Hz), 5.10 (2H,

s), 4.30-4.15 (4H, m), 2.76-2.69 (2H, m), 1.44 (9H, s).

Example 18: Synthesis of (3S)-3-amino-4-hydroxy-5-phenoxy-pentanoic acid t-butyl ester

Conventional hydrogenolysis of (3S)-3-phenylmethyloxycarbonylamino-4-hydroxy-5-phenoxy-pentanoic acid t-butyl ester (H_2 balloon, Pd/C, EtOH) gave the desired product (100%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.29-7.26 (2H, m), 6.97-6.90 (3H, m), 4.08-3.82 (3H, m), 3.43 (1H, m), 2.63-2.37 (2H+NH_2+OH, m), 1.46 and 1.45 (9H, two s).

The following compound was prepared similarly:

· (3S)-3-amino-4-hydroxy-5-(1-naphthyl)oxy-pentanoic acid t-butyl ester

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.22 (1H, m), 7.80 (1H, m), 7.50-7.34 (4H, m), 6.84 (1H, m), 4.26-4.20 (2H, m), 4.03-3.94 (1H, m), 3.51 (1H, m), 2.70-2.40 (2H, m), 1.47 and 1.46 (9H,. two s).

(F) Coupling of isoxazoline derivatives and aspartic acid derivatives and further transformations thereof (Examples 19 to 24).

Example 19: Synthesis of (2S)-2-{3-[(1S)-1-phenylmethyloxycarbonyl-amino-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-succinic acid 4-t-butyl ester 1-(N-methyl-N-methoxy) amide

A solution of 3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (502mg, 1.10 mmol) in THF (6.6 mL) was treated with 1N-NaOH (1.33mL). After stirring for 2.5h at room temperature, the reaction solution was quenched

with 1N-HCl (1.33 mL), then concentrated in vacuo. The residue together with sat'd NaCl(50 mL+ 2-3 mL의 1N-HCl) was extracted with ethyl acetate (100 mL x 2), dried (anh Na_2SO_4), filtered and concentrated to give 476mg (101 %) of 3-[(1S)-1-phenylmethyl-oxycarbonylamino-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carboxylic acid.

The crude acid (320 mg, 0.75 mmol) and β -t-butyl aspartic acid N-methyl- (N-methoxy) amide (209 mg, 1.2 eq) in DMF (5mL) at 0°C were treated with HOBt (122mg, 1.2 eq), EDC (172mg, 1.2 eq) and triethylamine (0.31 mL, 3.0 eq), and then stirred for 3h (0°C to room temperature). Concentration, conventional workup followed by flash chromatography gave less polar isomer (160mg) and more polar isomer (213mg, 33%).

More polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.64 (1H, d), 7.35-7.24 (7H, m), 6.95 (1H, t, J = 7.3 Hz), 6.88 (2H, d, J = 7.8 Hz), 5.55 (1H, d), 5.18-5.08 (3H, m), 4.44 (1H, m), 4.32-4.25 (2H, m), 3.75 (3H, s), 3.32-3.25 (2H, m), 3.12 (3H, s), 2.77-2.71(1H, m), 2.62-2.56 (1H, m), 2.12 (1H, m), 1.44 (9H, s), 1.03-0.91 (6H, m).

Less polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.65 (1H, d, J = 8.3 Hz), 7.36-7.23 (7H, m), 6.95 (1H, t, J = 7.3 Hz), 6.88 (2H, d, J = 8.3 Hz), 5.19-5.11 (4H, m), 4.46 (1H, m), 4.33-4.22 (2H, ABq, J =10.3 Hz), 3.75 (3H, s), 3.33 (2H, s), 3.23 (3H, s), 2.73 (1H, m), 2.57 (1H, m), 2.07 (1H, m), 1.43 (9H, s), 1.03-0.92 (6H, m).

Example 20: Synthesis of (3S)-3-{3-[(1S)-1-phenylmethyloxycarbonyl-amino-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-pentanoic acid t-butyl ester

The title compound was obtained from treatment of excess MeMgBr (3.0M

in ether, > 3.0 eq) to a solution of less polar isomer of (2S)-2-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxa-zole-5-carbonyl-amino}-succinic acid 4-t-butyl ester 1-(N-methyl-N-methoxy) amide (110 mg, 0.17 mmol) in THF (5 mL) + LiCl satuated THF (2 mL) at 0°C - room temperature (44mg, 43%).

From less polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.00 (1H, d, J = 9.3 Hz), 7.36-7.24 (7H, m), 6.96 (1H, t, J = 7.2 Hz), 6.87 (2H, d, J = 8.3 Hz), 5.26 (1H, d, J = 8.8 Hz), 5.12-5.09 (2H, m), 4.66 (1H, m), 4.43 (1H, d, J= 9.8 Hz), 4.21 (1H, d, J = 9.8 Hz0, 3.37-3.19 (2H, ABq, J = 18.0 Hz), 2.88 (1H, m), 2.58 (1H, m), 2.25 (3H, s), 2.03 (1H, m), 1.42 (9H, s), 0.99-0.89 (6H, m).

Similar treatment of more polar isomer of (2S)-2-{3-[(1S)-1-phenylmethyl-oxy-carbonylamino-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-succinic acid 4-t-butyl ester 1-(N-methyl-N-methoxy) amide (135 mg) gave 52mg (41%) of the corresponding methyl ketone.

Example 21: Synthesis of (2S)-2-{3-[2-methyl-(1S)-1-(naphthalene-2-carbonyl-amino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-succinic acid 4-t-butyl ester 1-methyl ester

A solution of 3-[2-methyl-(1S)-1-(naphthalene-2-carbonylamino)-propyl]-5-phenyl- methyl-4,5-dihydro-isoxazole-5-carboxylic acid (2.14g, 5.07 mmol), aspartic acid β -t-butyl ester methyl ester hydrochloride (1.46g, 1.2 eq), EDC (1.17g, 1.2 eq) and HOBt (822 mg, 1.2 eq) in DMF (19 mL) was treated with triethylamine (2.12 mL, 3.0 eq), and stirred overnight. Conventional workup followed by flash chromatography (40-50% ethyl acetate-hexanes) gave the title compound (2.94g, 94%) as a white foam.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.30 and 8.25 (1H, two s), 7.96-7.79 (4H, m), 7.65-7.54 (3H, m), 7.31-7.18 (5H, m), 6.76 (0.5H, d, J = 9.3 Hz), 6.43 (0.5H, d, J = 8.8 Hz), 4.96-4.70 (2H, m), 3.71 and 3.60 (3H, two s), 3.45-3.14 (4H, m), 3.08-2.34 (2H, m), 2.15 (1H, m), 1.47 and 1.44 (9H, two s), 1.04-0.88 (6H, m).

The above compound was hydrolyzed according to the above described method (1N-NaOH in THF) to obtain the coresponding carboxylic acid (100%).

The following esters and free carboxylic acids were prepared similarly.

· (2S)-2-{3-[2-methyl-(1S)-1-(naphthalene-2-carbonylamino)-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-succinic acid 4-t-butyl ester 1-methyl ester

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.33 and 8.30 (1H, two s), 7.95-7.74 (5H, m), 7.59-7.53 (2H, m), 7.28-7.22 (2H, m), 6.99-6.89 (3.5H, m), 6.71 (0.5H, d, J = 8.8 Hz), 5.08-5.01 (1H, m), 4.83-4.79 (1H, m), 4.39-4.29 (2H, m), 3.76 and 3.64 (3H, two s), 3.44 (2H, s), 2.97-2.93 (1H, m), 2.74-2.69 (1H, m), 2.34-2.23 (1H, m), 1.45 and 1.42 (9H, two s), 1.15-1.01 (6H, m).

Hydrolysis of the above compound gave free carboxylic acid.

· (2S)-2-{3-[(1S)-1-(phenylmethyloxycarbonyl)-amino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonyl-amino}-succinic acid 4-t-butyl ester 1-methyl ester

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.59-7.49 (1H, m), 7.38-7.32 (5H, m), 5.25-4.95 (4H, m), 4.86 (1H, m), 4.48 (1H, m), 3.76 and 3.67 (3H, two

s), 3.29 (2H, m), 2.92 (1H, m), 2.71-2.62 (1H, m), 2.04 (1H, m), 1.48 (9H, s), 1.01-0.85 (6H, m)

· (2S)-2-{3-[(1S)-1-phenethylcarbonylamino-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-succinic acid 4-t-butyl ester-1-methyl ester (diastereomeric)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 8.3 Hz, 0.5H), 7.47 (d, J = 9.3 Hz, 0.5 H), 7.28-7.18 (m, 10H), 5.83 & 5.44 (two d, J = 8.8 Hz, 1H), 4.70-4.52 (m, 2H), 3.68 & 3.65 (two s, 3H), 3.33-2.28 (m, 10H), 1.89 (m, 1H), 1.43 & 1.42 (two s, 9H), 0.79-0.63 (m, 6H).

· (2S)-2-{3-[(1S)-1-(1-naphthalenecarbonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-succinic acid 4-t-butyl ester-1-methyl ester (diastereomeric)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.27 (m, 1H), 7.92-7.85 (m, 2H), 7.61-7.15 (m, 10H), 6.45 & 6.05 (two d, NH), 4.99-4.85 (m, 1H), 4.70 (m, 1H), 3.69 & 3.52 (two s, 3H), 3.50-2.32 (m, 6H), 2.12 (m, 1H), 1.40 & 1.39 (two s, 9H), 1.05-0.80 (m, 6H).

· (2S)-2-{3-[(1S)-1-(1-naphthalenesulfonylamino-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-succinic acid 4-t-butyl ester-1-methyl ester (diastereomeric)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.69-8.62 (m, 1H), 8.33-7.94 (m, 3H), 7.70-7.47 (m, 3H), 7.20-7.05 (m, 5H), 5.32 & 5.15 (two m, 1H), 4.68 & 4.54 (two m, 1H), 3.85 & 3.59 (two m, 1H), 3.82 & 3.62 (two s, 3H), 3.23-1.75 (m, 7H), 1.40 & 1.34 (two s, 9H), 0.85-0.48 (m, 6H).

· (2S)-2-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-succinic acid 4-t-butyl ester-

1-methyl ester (diastereomeric)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.53-7.49 (two d, 1H), 7.35-7.25 (m, 10H), 5.09-5.07 (m, 2.5 H), 4.88 (d, 0.5 H), 4.69 (m, 1H), 4.34 & 4.23 (two m, 1H), 3.68 &3.63 (two s, 3H), 3.36-2.23 (m, 6H), 1.89 & 1.70 (two m, 1H), 1.42 & 1.40 (two s, 9H), 0.88-0.73 (m, 6H).

· (2S)-2-{3-[(1S)-1-(indole-3-yl-ethylcarbonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-succinic acid 4-t-butyl ester-1-methyl ester (diastereomeric)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.54 & 8.38 (two br s, 1H), 7.62-6.97 (m, 1H), 5.83 (d, J = 8.8 Hz, 0.5H), 5.20 (d, J = 9.3 Hz, 0.5H), 4.73-4.69 (m, 1H), 4.61 & 4.48 (two m, 1H), 3.71 & 3.59 (two s, 3H), 3.28-2.26 (m, 10H), 1.87-1.75 (m, 1H), 1.43 &1.42 (two s, 9H), 0.78-0.50 (m, 6H).

· (2S)-2-{3-[(1S)-1-(indole-3-yl-methylcarbonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-succinic acid 4-t-butyl-ester-1-methyl ester (diastereomeric)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.37 & 8.26 (two br s, 1H), 7.54-7.12 (m, 11H), 5.95 (d, J = 8.8 Hz, 0.5H), 5.76 (d, J = 1.5 Hz, 0.5H), 4.68-4.51 (m, 2H), 3.78-3.68 (m, 2H), 3.66 & 3.62 (two s, 3H), 3.28-2.21 (m, 6H), 1.80 (m, 1H), 1.41 & 1.37 (two s, 9H), 0.75-0.46 (m, 6H).

· (2S)-2-{3-[(1S)-1-(cinnamoylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-succinic acid 4-t-butyl ester-1-methyl ester (diastereomeric)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.63-7.25 (m, 12H), 6.43-6.32 (two d, J = 15.6 Hz, 1H), 6.09 & 5.68 (two d, J = 9.3 Hz, 1H), 4.78-4.70 (m, 1H), 3.69 & 3.68 (two s, 3H), 3.35-2.31 (m, 6H), 2.03 (m, 1H), 1.43 & 1.40

(two s, 9H), 0.92-0.76 (m, 6H).

. (2S)-2-{3-[(1S)-1-(phenylmethylsulfonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-succinic acid 4-t-butyl ester-1-methyl ester (diastereomeric)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.67 & 7.60 (two d, J = 8.8 Hz, 1H), 7.40-7.17 (m, 10H), 3.71 & 3.55 (two s, 3H), 3.37-2.23 (m, 6H), 1.70 (m, 1H), 1.42 & 1.47 (two s, 9H), 0.91-0.65 (m, 6H).

Example 22: Synthesis of (3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-2-carbonyl-amino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid-t-butyl ester

A solution of (2S)-2-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-4,5-dihydro-5-phenylmethyl-isoxazole-5-carbonyl-amino}-succinic acid 4-t-butyl ester (2.86g, 4.75 mmol) and NMM (0.57 mL, 1.1 eq) in dry THF (x mL) under N_2 at 0°C was treated with isobutyl chloroformate (0.65 mL, 1.05eq), and stirred for 20 min. To the solution at 0°C was added diazomethane, and stirred for 30 min. (TLC analysis). Additional diazomethane was needed to complete the reaction(1h). After completion of the diazoketone formation, 30% HBr/AcOH (4.0 mL, 4.0 eq) was added at 0 °C and the reaction was stirred for 1h. The reaction was extracted with ethyl acetate (x2) and the organic layer was washed with water, sat'd $NaHCO_3$ and brine, dried (anh Na_2SO_4), filtered and concentrated to give 3.36g of a yellow solid. Half of the solid (~2.375 mmol) was reacted with anhydrous KF (345 mg, 2.5 eq) and 2,6-dichlorobenzoic acid (545 mg, 1.2 eq) in DMF (10 mL) under N_2 at room temperature. Usual workup followed by flash chromatography gave the title compound as diastereomeric mixture (1.53g). Preparative HPLC (38% EtOAc/Hexane)

gave less polar diastereomer (585 mg) and more polar diastereomer (358mg).

Less polar diastereomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.28 (1H, s), 7.84-7.80 (4H, m), 7.55-7.46 93H, m), 7.29-7.24 98H, m), 6.87 (1H, d, J = 8.8 Hz), 5.05-4.93 (3H, m), 4.73 (1H, m), 3.54 (1H, d, J = 18.1 Hz), 3.34 (1H, d, J = 13.7 Hz), 3.19 (1H, d, J = 14.2 Hz), 3.11 (1H, d, J = 17.6 Hz), 2.74-2.70 (1H, m), 2.29-2.24 (2H, m), 1.39 (9H, s), 1.02 (3H, d, J = 6.4 Hz), 0.92 (3H, d, J = 6.8 Hz).

More polar diastereomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.28 (1H, s), 7.97-7.75 (5H, m), 7.62-7.57 (2H, m), 7.37-7.22 (8H, m), 6.56 (1H, d, J = 8.3 Hz), 4.94 (1H, m), 4.78 (1H, m), 4.51-4.42 (2H, m), 3.51-3.43 (2H, m), 3.24-3.15 (2H, m), 2.99-2.95 (1H, m), 2.56-2.52 (1H, m), 2.18 (1H, m), 1.45 (9H, s), 1.02 (3H, d, J = 6.8 Hz), 0.97 (3H, d, J = 6.4 Hz).

The following compounds were prepared similarly.

· (3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-2-carbonylamino)-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid-t-butyl ester

Less polar diastereomer : ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.29 (1H, s), 7.85-7.81 (5H, m), 7.54-7.46 (2H, m), 7.31-7.23 (5H, m), 6.98-6.87 (4H, m), 5.13-5.03 (3H, m), 4.90 (1H, m), 4.39-4.27 (2H, ABq, J = 9.3 Hz), 3.51 (1H, d, J = 17.6 Hz), 3.41 (1H, d, J = 17.6 Hz), 2.94-2.78 (2H, m), 2.38 (1H, m), 1.41 99H, s), 1.12-1.08 (6H, two d, J = 6.4 Hz).

More polar diastereomer : ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.30 (1H, s), 8.11 (1H, d, J = 8.8 Hz), 7.93-7.83 (4H, m), 7.59-7.53 (2H, m), 7.33-7.22 (5H, m), 6.97-6.91 (3H, m), 6.77 (1H, d, J = 8.8 Hz), 5.37 (1H, d, J = 17.1 Hz), 5.16 (1H, d, J = 17.1 Hz), 5.01-4.95 (2H, m), 4.53 (1H, d, J = 9.8 Hz), 4.25 (1H, d, J = 9.8 Hz), 3.50 (1H, d, J = 7.6 Hz), 3.32 (1H, d,

J = 7.6 Hz), 3.04-3.00 (1H, dd, J = 17.1, 4.9 Hz), 2.73-7.68 (1H, dd, 17.1, 5.4 Hz), 2.24 (1H, m), 1.47 (9H, s), 1.10-1.03 (6H, two d, J = 6.4 Hz).

· (3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid-t-butyl ester (diastereomeric mixture)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.72-7.60 (1H, m), 7.37-7.30 (8H, m), 5.40 (0.5H, d), 5.23-4.85 (6.5H, m), 4.40 (1H, m), 3.30 (2H, m), 2.92-2.65 (2H, m), 2.10-1.98 (1H, m), 1.44 (9H, s), 1.00-0.87 (6H, m).

Following compounds were similarly prepared:

· (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid t-butyl ester

More polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.59 (d, J = 8.7 Hz, 1H), 8.31 (d, J = 8.3 Hz, 1H), 8.26 (d, J = 8.7 Hz, 1H), 8.13 (d, J = 8.7 Hz, 1H), 7.98 (d, J = 8.7 Hz, 1H), 7.88 9d, J = 7.8 Hz, 1H), 7.78 (m, 1H), 7.63 (m, 1H), 7.22-7.15 (m, 4H), 6.96-6.81 (m, 6H), 4.99-4.81 (m, 4H), 4.40 (d, J = 10.1 Hz, 1H), 4.21 (d, J = 10.0 Hz, 1H), 3.44 (d, J = 17.9 Hz, 1H), 3.24 (d, J = 17.9 Hz, 1H), 3.03 (dd, J = 17.0, 4.6 Hz, 1H), 2.76 (dd, J = 17.0, 5.5 Hz, 1H), 2.30(m, 1H), 1.45 (s, 9H), 1.10 (m, 6H)

Less polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.68 (d, J = 8.7 Hz, 1H), 8.32-8.26 (m, 2H), 8.17 (d, J = 8.7 Hz, 1H), 7.91 (m, 2H), 7.80 (m, 1H), 7.66 (m, 1H), 7.28 (m, 4H), 7.02-6.87 (m, 6H), 5.01-4.77 (m, 4H), 4.38-4.30 (m, 2H), 3.50-3.38 (ABq, J = 17.9 Hz, 2H), 3.06-3.02 (m, 1H), 2.84-2.80 (m, 1H), 2.34 (m, 1H), 1.44 (s, 9H), 1.14 (m, 6H)

· (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenoxymethy-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid.

From more polar isomer: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.01 (d, J = 9.2 Hz, 1H), 8.87 (d, J = 8.3 Hz, 1H), 8.55 (d, J = 8.3 Hz, 1H), 8.18-8.07 (m, 3H), 7.87 (m, 1H), 7.73 (m, 1H), 7.28-7.14 (m, 4H), 6.96-6.75 (m, 6H), 5.00-4.75 (m, 4H), 4.42 (d, J = 10.6 Hz, 1H), 4.22 (d, J = 10.6 Hz, 1H), 3.47-3.35 (ABq, J = 17.9 Hz, 2H), 2.82 (dd, J = 17.0, 6.4 Hz, 2.56 (m, 1H), 2.33 (m, 1H), 0.98 (m, 6H).

From less polar isomer: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.06 (d, J = 9.2 Hz, 1H), 8.88 (d, J = 7.8 Hz, 1H), 8.57 (d, J = 8.7 Hz, 1H), 8.22-8.07 (m, 3H), 7.87 (m, 1H), 7.73 (m, 1H), 7.17 (m, 4H), 6.91-6.78 (m, 6H), 4.98-4.90 (ABq, J = 17.9 Hz, 2H), 4.77 (m, 2H), 4.35 (d, J = 10.6 Hz, 1H), 4.20 (d, J = 10.6 Hz, 1H), 3.47-3.35 (ABq, J = 18.3 Hz, 2H), 2.89 (dd, J = 17.0, 6.4 Hz, 2.61 (dd, J =17.0, 6.4, 1H), 2.31 (m, 1H), 0.98 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenecarbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid t-butyl ester

More polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.29 (d, J = 8.3 Hz), 7.94 (d, J = 8.3 Hz), 7.88 (d, J = 7.4 Hz, 1H), 7.74 (d, J = 9.7 Hz, 1H), 7.61-7.44 (m, 4H), 7.35-7.18 (m, 8H), 6.23 (d, J = 8.7 Hz, 1H), 4.95 (m, 1H), 4.76 (m, 1H), 4.49-4.41 (ABq, J = 17.5 Hz, 2H), 3.49-3.41 (m, 2H), 3.22-3.12 (m, 2H), 2.92 (dd, J = 17.0, 4.2 Hz, 1H), 2.52 (dd, J = 17.0, 5.1 Hz, 1H), 2.13 (m, 1H), 1.37 (s, 9H), 1.04 (d, J = 6.9 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H).

Less polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J = 8.3 Hz,

1H), 7.83 (m, 2H), 7.57-7.47 (m, 4H), 7.38-7.22 (m, 9H), 6.64 (d, J = 9.2 Hz, 1H), 5.00-4.87 (m, 3H), 4.72 (m, 1H), 3.60 (d, J = 17.9 Hz, 1H), 3.36 (d, J = 14.2 Hz, 1H), 3.20 (d, J = 14.2 Hz, 1H), 3.12 (d, J = 17.9 Hz, 1H), 2.69 (dd, J = 17.0, 4.6 Hz, 1H), 2.28-2.18 (m, 2H), 1.38 (s, 9H), 1.06 (d, J = 6.4 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(cinnamoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid t-butyl ester (more polar isomer)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.72 (d, 1H), 7.62 (d, J = 15.6 Hz, 1H), 7.50 (m, 1H), 7.38-7.21 (m, 12H), 6.39 (d, J = 15.6 Hz, 1H), 5.90 (d, J = 9.2 Hz, 1H), 4.76 (m. 2H), 4.49-4.41 (ABq, J = 17.4 Hz, 2H), 3.42-3.38 (m, 2H), 3.17 (d, J = 14.2 Hz, 1H), 3.09 (d, J = 17.9 Hz, 1H), 2.91 (dd, J = 17.4, 4.6 Hz, 1H), 2.52 (dd, J = 17.4, 5.0 Hz, 1H), 2.04 (m, 1H), 1.41 (s, 9H), 0.90 (m, 6H).

Less polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.61 (d, 1H), 7.52 (d, 1H), 7.41 (d, 1H), 7.28 (m, 12H), 6.64-6.41 (m, 2H), 5.09-4.99 (ABq, J = 17.4 Hz, 2H), 4.81 (m, 1H), 4.69 (m, 1H), 3.50 (d, J = 17.9 Hz, 1H), 3.34 (d, J = 14.2 Hz, 1H), 3.17 (d, J = 14.2 Hz, 1H), 3.04 (d, J = 17.9 Hz, 1H), 2.74 (dd, J = 17.0, 4.2 Hz, 1H), 2.22 (m, 2H), 1.39 (s, 9H), 0.97-0.88 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(phenylmethylsulfonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid t-butyl ester

More polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 9.3 Hz, 1H), 7.38-7.23 (m, 13H), 4.80-4.63 (m, 2H), 4.56-4.46 (ABq, J = 17.1 Hz, 2H), 4.21-4.10 (m, 2H), 3.83 (m, 2H), 3.41-3.37 (m, 1H), 3.19 (d, J = 14.2 Hz, 1H), 2.90-2.83 (m, 2H), 2.53 (m, 1H), 1.76 (m, 1H), 1.41 (s,

9H), 0.83 (d, J = 6.8 Hz, 3H), 0.77 (d, J = 6.8 Hz, 3H).
Less polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 9.2 Hz, 1H), 7.36-7.26 (m, 13H), 5.05-4.95 (m, 3H), 4.74 (m, 1H), 4.17 (m, 2H), 3.96 (m, 1H), 3.41-2.99 (m, 4H), 2.70 (m, 1H), 2.19 (m, 1H), 1.79 (m, 1H), 1.39 (s, 9H), 0.86 (d, J = 6.4 Hz, 3H), 0.77 (d, J = 6.8 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid t-butyl ester

More polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.59 (d, J = 8.7 hz, 1H), 8.31 (d, J = 8.7 Hz, 1H), 8.26 (d, J = 8.7 Hz, 1H), 8.12 (d, J = 8.3 Hz, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.78-7.72 (m, 2H), 7.62 (m, 1H), 7.33-7.27 (m, 3H), 5.20-5.05 (m, 3H), 4.92-4.89 (m, 2H), 3.47-3.34 (m, 2H), 2.95 (dd, J = 17.0, 4.6 Hz, 1H), 2.73 (dd, J = 17.0, 5.1 Hz, 1H), 2.28 (m, 1H), 1.45 (s, 9H), 1.07 (m, 6H).
Less polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.58 (d, J = 9.2 Hz, 1H), 8.28-8.24 (m, 2H), 8.12 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.75-7.59 (m, 3H), 7.31-7.25 (m, 3H), 5.12-4.89 (m, 5H), 3.46-3.41 (m, 2H), 2.92 (dd, J = 17.0, 5.1 Hz, 1H), 2.78 (dd, J = 17.0, 5.5 Hz, 1H), 2.30 (m, 1H), 1.44 (s, 9H), 1.10 (m, 6H)

· (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid t-butyl ester

More polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.52 (d, J = 9.2 Hz, 1H), 8.32 9d, J = 8.3 Hz, 1H), 8.26 (d, J = 8.3 Hz, 1H), 8.12 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.80-7.63 (m, 3H), 7.36-7.18 (m, 8H), 4.82 (m, 1H), 4.72 (m, 1H), 4.47-4.37 (ABq, J = 17.0 Hz, 2H), 3.47 (d, J = 17.9 Hz, 1H), 3.41 (d, J = 13.8 Hz, 1H), 3.19 (d, J = 14.2 Hz,

1H), 3.14 (d, J = 17.9 Hz, 1H), 2.94 (dd, J = 17.4, 4.1 Hz, 1H), 2.53 (dd, J = 17.0, 5.0 Hz, 1H), 2.18 (m, 1H), 1.45 (s, 9H), 0.98 (m, 6H).

Less polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.52 (d, J = 9.2 Hz, 1H), 8.28-8.23 (m, 2H), 8.12 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 8.3 Hz, 1H), 7.73 (m, 1H), 7.62-7.55 (m, 2H), 7.31-7.17 (m, 8H), 5.06-4.98 (ABq, J = 17.0 Hz, 2H), 4.84 (m, 1H), 4.69 (m, 1H), 5.54 (d, J = 17.9 Hz, 1H), 3.29 (d, J = 14.2 H, 1H), 3.16 (d, J = 14.2 Hz, 1H), 3.10 (d, J = 17.9 Hz, 1H), 2.70 (dd, J = 17.0, 4.1 Hz, 1H), 2.21 (m, 1H), 2.11 (dd, J = 17.0, 5.1 Hz, 1H), 1.38 (s, 9H), 0.98 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid t-butyl ester

More polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.47 (d, J = 9.2 Hz, 1H), 8.32 (d, J = 8.7 Hz, 1H), 8.25 (d, J = 8.3 Hz, 1H), 8.13 (d, J = 8.7 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.78 (m, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.64 (t, J = 7.3 Hz, 1H), 7.29-7.17 (m, 4H), 7.06 (t, J = 7.4 Hz, 1H), 6.96 (t, J = 7.4 Hz, 1H), 6.78 (d, J = 8.3 Hz, 2H), 4.81-4.72 (m, 2H), 4.47-4.28 (ABq, J = 17.9 Hz, 2H), 3.42 (d, J = 17.9 Hz, 1H), 3.34 (d, J = 14.2 Hz, 1H), 3.15 (d, J = 13.7 Hz, 1H), 3.10 (d, J = 17.9 Hz, 1H), 2.94 (dd, J = 17.4, 4.1 Hz, 1H), 2.64 (dd, J = 17.4, 5.5 Hz, 1H), 2.15 (m, 1H), 1.43 (s, 9H), 0.95 (m, 6H).

Less polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.50 (d, J = 9.2 Hz, 1H), 8.24 (d, J = 8.3 Hz, 1H), 8.18 (d, J = 8.3 Hz, 1H), 8.10 (d, J = 8.2 Hz, 1H), 7.85 (d, J = 7.7 Hz, 1H), 7.74 (m, 1H), 7.62-7.56 (m, 2H), 7.29-7.16 (m, 5H), 6.88 (t, J = 7.4 Hz, 1H), 6.78 (d, J = 7.8 Hz, 2H), 4.81-4.66 (m, 4H), 3.46 (d, J = 17.9 Hz, 1H), 3.29 (d, J = 13.8 Hz, 1H), 3.15 (d, J = 13.8 Hz, 1H), 3.07 (d, J = 17.9 Hz, 1H), 2.76 (dd, J = 17.0, 4.1 Hz, 1H), 2.21-2.09 (m, 2H), 1.37 (s, 9H), 0.93 (m, 6H).

. (3S)-3-{3-[2-methyl-(1S)-1-(2-naphthalenecarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid t-butyl ester

Diastereomeric mixture: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.29 (m, 1H), 7.96-7.50 (m, 7H), 6.85-6.73 (m, 1H), 5.10-4.97 (m, 2H), 4.66 (m, 1H), 3.40 (m, 2H), 2.94-2.60 (m, 2H), 2.32-2.14 (m, 1H), 2.22 & 2.10 (two s, 3H), 1.43 & 1.42 (two s, 9H), 1.10-0.95 (m, 6H).

Example 23: Synthesis of (3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-2-carbonyl-amino)-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-5-phenoxy-pentanoic acid t-butyl ester

The title compound was prepared with conventional EDC coupling of 3-[2-methyl-(1S)-1-(naphthalene-2-car-bonylamino)-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carboxylic acid (1.00g, 2.24 mmol) and (3S)-3-amino- 4-hydroxy-5- phenoxy-pentanoic acid t-butyl ester (630 mg, 1.0 eq), EDC (558 mg, 1.3 eq), HOBt(394 mg, 1.3 eq) and triethylamine (0.94 mL, 3.0 eq) in DMF (5 mL). Usual workup followed by flash chromatography gave 1.44g of coupled product. The coupled product and Dess-Martin reagent (2.15g, 2.5 mol eq) in dry CH_2Cl_2 (25mL) under N_2 at room temperature was stirred for 1h, then quenched with isopropyl alcohol(3 mL). Usual extractive workup followed by flash chromatography (36% ethyl acetate-hexane) gave 1.27g of the title compound as diastereomeric mixture. Preparative HPLC (36% ethyl acetate-hexanes, 10 mL/min, 278 nm UV detection) afforded less polar (352 mg) and more polar (536 mg) diastereomers.

Less polar diastereomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.29 (1H, s), 7.93-7.81 (5H, m), 7.58-7.51 (2H, m), 7.28-7.21 94H, m), 6.99-6.76 (7H, m), 5.00-4.98 (2H, m), 4.79-4.66 (2H, ABq, J = 16.6 Hz), 4.35-4.29 (2H,

ABq, J = 10.3 Hz), 3.40 (2H, s), 3.02-2.98 (1H, dd, J = 16.6, 4.9 Hz), 2.84-2.79 (1H, dd, J = 16.6, 4.7 Hz), 2.30 (1H, m), 1.41 (9H, s), 1.12-1.07 (6H, two d, J = 6.8 Hz).

More polar diastereomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.29 (1H, s), 7.99-7.82 (5H, m), 7.59-7.53 (2H, m), 7.26-7.18 (4H, m), 6.97-6.83 (6H, m), 6.68 (1H, d, J = 8.3 Hz), 5.01-4.95 (3H, m), 4.83 (1H, d, J = 17.1 Hz), 4.42 (1H, d, J = 9.8 Hz), 4.23 (1H, d, J = 9.8 Hz), 3.49-3.32 (2H, ABq, J = 18.1 Hz), 3.06-3.02 (1H, dd, J = 17.1, 4.4 Hz), 2.76-2.72 (1H, dd, J = 17.1, 5.4 Hz), 2.24 (1H, m), 1.45 (9H, s), 1.10-1.02 (6H, two d, J = 6.8 Hz).

The following compounds were prepared similarly:

· (3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-2-carbonylamino)-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-5-(2-naphthyloxy)-pentanoic acid-t-butyl ester

Less polar diastereomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.27(1H, s), 7.89 (8H, m), 7.56-7.26 (6H, m), 7.23-6.87 (5H, m), 6.74 (1H, d, J = 9.3 Hz), 5.04-4.95 (2H, m), 4.92-4.80 (2H, ABq, J = 16.6 Hz), 4.37-4.30 (2H, ABq, J = 23.4, 10.3 Hz), 3.43-3.38 (2H, ABq, J = 22.5, 17.8 Hz), 3.05-3.00 (1H, dd, J = 16.6, 4.9 Hz), 2.86-2.82 (1H, dd, J = 16.6, 4.9 Hz), 2.25 (1H, m), 1.42 (9H, s), 1.09-1.05 (6H, two d, J = 6.8, 6.7 Hz).

More polar diastereomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.30 (1H, s), 8.02-7.55 (10H, m), 7.41-7.05 (6H, m), 6.89-6.66 (4H, m), 5.10-4.94 (4H, m), 4.41 (1H, d, J = 9.8 Hz), 4.23 91H, d, J = 10.3 Hz), 3.50-3.34 (2H, ABq, J = 17.6 Hz), 3.09-3.05 (1H, dd, J = 17.1, 4.4 Hz), 2.79-2.74 (1H, dd, J = 17.1, 5.4 Hz), 2.25 (1H, m), 1.45 (9H, s), 1.10-1.02 (6H, two d, J = 6.8 Hz).

· (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid t-butyl ester More polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.60 (d, J = 9.2 Hz, 1H), 8.32-8.25 (m, 2H), 8.13 (d, J = 8.8 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.79-7.62 (m, 3H), 7.27 (m, 2H), 6.97 (m, 1H), 6.88 (m, 2H), 5.04-4.72 (m, 5H), 3.48-3.34 (m, 2H), 3.00 (dd, J = 17.0, 4.6 Hz, 1H), 2.77 (dd, J = 17.0, 5.5 Hz, 1H), 2.27 (m, 1H), 1.45 (s, 9H), 1.06 (m, 6H).

Less polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.58 (d, J = 9.2 Hz, 1H), 8.27 (d, J = 8.2 Hz, 1H), 8.21 (d, J = 8.3 Hz, 1H), 8.13 (d, J = 8.3 Hz, 1H), 7.86 (d, J = 8.3 Hz, 1H), 7.78-7.59 (m, 3H), 7.22 (m, 2H), 6.92 (m, 1H), 6.82 (m, 2H), 5.04-4.88 (m, 3H), 4.82-4.69 (ABq, J = 17.0 Hz, 2H), 3.45-3.33 (m,2H), 2.99 (dd, J = 16.5, 4.6 Hz, 1H), 2.78 (dd, J = 16.5, 5.1 Hz, 1H), 2.26 (m, 1H), 1.42 (s, 9H), 1.06 (m, 6H)

· t-Butyl (3S)-3-{3-[2-methyl-(1S)-1-(3-t-butyloxycarbonylpropanoylamino)-propyl]-5-n-pentyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoate; less polar isomer (Compound 89LP precursor) ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.7 Hz, 1H), 7.32 (m, 3H), 6.42 (m, 1H), 5.20-5.05 (ABq, J = 17.0 Hz, 2H), 4.90 (m, 1H) 4.67 (m, 1H), 3.38 (d, J = 17.9 Hz, 1H), 2.92 (m, 2H), 2.78 (m, 1H), 2.53 (m, 2H), 2.40 (m, 2H), 2.18 (m, 1H), 2.03 (m, 1H), 1.79 (m, 1H), 1.44 (s, 9H), 1.41 (s, 9H), 1.26 (m, 6H), 0.94 (m, 6H), 0.86 (t, J = 6.9 Hz, 3H).

· t-Butyl (3S)-3-{3-[2-methyl-(1S)-1-(3-t-butyloxycarbonylpropanoylamino)-propyl]-5-n-pentyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoate; more polar isomer (Compound 90MP precursor) ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.7 Hz, 1H), 7.31 (m, 3H), 6.17 (d, J = 8.7 Hz, 1H), 5.17-5.07 (ABq, J = 17.0 Hz, 2H), 4.87 (m,

1H) 4.65 (m, 1H), 3.30 (d, J = 17.9 Hz, 1H), 2.96-2.90 (m, 2H), 2.69 (m, 1H), 2.56 (m, 2H), 2.45 (m, 2H), 2.03 (m, 2H), 1.81 (m, 1H), 1.43 (s, 9H), 1.41 (s, 9H), 1.26 (m, 6H), 0.94-0.86 (m, 9H).

· t-Butyl (3S)-3-{3-[2-methyl-(1S)-1-(3-t-butyloxycarbonylpropanoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoate; less polar isomer (Compound 85LP precursor)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 9.2 Hz, 1H), 7.34-7.22 (m, 8H), 6.37 (d, J = 9.2 Hz, 1H), 5.10-4.98 (ABq, J = 17.4 Hz, 2H), 4.70 (m, 1H) 4.61 (m, 1H), 3.46 (d, J = 17.9 Hz, 1H), 3.31 (d, J = 14.2 Hz, 1H), 3.14 (d, J = 14.2 Hz, 1H), 2.99 (d, J = 17.9 Hz, 1H), 2.73 (m, 1H), 2.53 (m, 2H), 2.40 (m, 2H), 2.18 (m, 1H), 2.09 (m, 1H), 1.42 (s, 9H), 1.39 (s, 9H), 0.90 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.4 Hz, 3H).

· t-Butyl (3S)-3-{3-[2-methyl-(1S)-1-(3-t-butyloxycarbonylpropanoylamino)-propyl]-5-ethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoate; less polar isomer (Compound 91LP precursor)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 8.7 Hz, 1H), 7.32 (m, 3H), 6.42 (d, J = 9.2, 1H), 5.21-5.05 (ABq, J = 17.0 Hz, 2H), 4.91 (m, 1H) 4.67 (m, 1H), 3.37 (d, J = 17.9 Hz, 1H), 2.94 (m, 2H), 2.79 (m, 1H), 2.53 (m, 2H), 2.40 (m, 2H), 2.18 (m, 1H), 2.07 (m, 1H), 1.86 (m, 1H), 1.43 (s, 9H), 1.41 (s, 9H), 0.94 (m, 9H).

· t-Butyl (3S)-3-{3-[2-methyl-(1S)-1-(3-t-butyloxycarbonylpropanoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoate; less polar isomer (Compound 73LP precursor)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 8.7 Hz, 1H), 7.32 (m, 3H),

6.44 (d, J = 9.2, 1H), 5.20-5.04 (ABq, J = 17.0 Hz, 2H), 4.88 (m, 1H) 4.67 (m, 1H), 3.46 (d, J = 17.9 Hz, 1H), 2.94-2.76 (m, 3H), 2.53 (m, 2H), 2.40 (m, 2H), 2.19 (m, 1H), 1.62 (s, 3H), 1.43 (s, 9H), 1.41 (s, 9H), 0.95 (m, 6H).

t-Butyl (3S)-3-{3-[2-methyl-(1S)-1-(3-t-butyloxycarbonylpropanoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlor obenzoyloxy)-pentanoate; more polar isomer (compound 74MP precursor)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 8.7 Hz, 1H), 7.33 (m, 3H), 6.18 (d, J = 8.7 Hz, 1H), 5.18-5.05 (ABq, J = 16.5 Hz, 2H), 4.87 (m, 1H) 4.65 (m, 1H), 3.38 (d, J = 17.9 Hz, 1H), 2.93-2.89 (m, 2H), 2.71 (m, 1H), 2.57 (m, 2H), 2.46 (m, 2H), 2.02 (m, 1H), 1.66 (s, 3H), 1.58 (s, 9H), 1.46 (s, 9H), 0.95-0.86 (m, 6H).

t-Butyl (3S)-3-{3-[2-methyl-(1S)-1-(3-t-butyloxycarbonylpropanoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoate; more polar isomer (Compound 86MP precursor)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 9.2 Hz, 1H), 7.30 (m, 8H), 6.07 (d, J = 8.7 Hz, 1H), 4.72 (m, 1H), 4.60 (m, 1H), 4.45-4.36 (ABq, J = 17.0 Hz, 2H), 3.40-3.32 (m, 2H), 3.17 (d, J = 14.2 Hz, 1H), 3.06 (d, J = 17.9 Hz, 1H), 2.93 (m, 1H), 2.60-2.38 (m, 5H), 1.98 (m, 1H), 1.44 (s, 9H), 1.41 (s, 9H), 0.88-0.82 (m, 6H).

Example 24: Synthesis of (3S)-3-{3-[(1S)-1-benzyloxycarbonylamino-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-pentanoic acid

A solution of (3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-

propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-pent anoic acid t-butyl ester (less polar diastereomer) (44mg) in CH_2Cl_2 (2 mL) at 0°C was treated with TFA (1 mL). The reaction mixture was stirred for 2h while slowly warming to room temperature. Concentration gave the title compound (compound 10, quantitative)

^1H NMR (500 MHz, CD_3OD) δ 7.35-6.90 (10H, m), 5.11 (2H, s), 4.53 (1H, m), 4.47 (1H, m), 4.23 (2H, dd), 2.86 (1H, dd), 2.54 (1H, dd), 2.24 (3H, s), 2.00 (1H, m), 1.00 and 0.97 (6H, two d); MS $[M+Na]^+$ 562

The following compound was prepared similarly from the less polar isomer:

· (3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenox ymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-pentanoic acid (compound 11).

^1H NMR (500 MHz,) δ 8.76 (1H,d, J = 7.8 Hz), 7.76 (1H, d, J = 8.8 Hz), 7.36-6.87 (10H, m), 5.06 (2H, m), 4.50 (1H, m), 4.32 (1H, m), 4.16 (2H, m), 3.21 (2H, app s), 2.79 (1H, m), 2.06 (3H, s), 1.89 (1H, m), 0.91 (3H, d, J = 6.3 Hz), 0.80 (3H, d, J = 6.3 Hz).

The following final compounds were obtained by a similar TFA deprotection of the corresponding t-butyl ester.

· (3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihy dro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid (compound 3, diastereomeric mixture)

^1H NMR (500 MHz, DMSO-d_6) δ 8. 49 (1H, m), 7.72 (1H, m), 7.35 (5H, m), 5.03 (3H, m), 4.40 (1H, m), 4.15 (1H, m), 3.24 (2H, m), 2.54 (2H, m), 2.04 and 1.95 (3H, wo s), 1.88 (1H, m), 0.90-0.81 (6H, m): MS $[M+Na]^+$ 456

· (3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (compound 14, diastereomeric mixture)

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (1H, br s), 7.75 (1H, m), 7.61-7.30 (8H, m), 5.30-5.00 (5H, m), 4.70 (1H, m), 4.16 (1H, m), 2.66 (2H, m), 1.90 (1H, m), 0.95-0.79 (6H, m): MS $[M+Na]^+$ 644

· (3S)-3-{3-[(1S)-1-(naphthalene-1-carbonylamino)-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (compound 17, diastereomeric mixture)

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.92-8.55 (2H, m), 8.15-7.98 (3H, m), 7.63-7.55 (4H, m), 7.25-7.15 (4H, m), 6.95-6.74 (6H, m), 5.20-4.15 (6H, m), 2.80-2.55 (2H, m), 2.05 (1H, m), 1.05-0.89 (6H, m): MS $[M+Na]^+$ 674.

· (3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (compound 18)

From less polar t-butyl ester: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.93 (1H, d, J = 7.8 Hz), 8.79 (1H, d, J = 8.3 Hz), 8.48 (1H, s), 8.05-7.94 (4H, m), 7.64-7.58 (2H, m), 7.30-7.17 (4H, m), 6.94-6.83 (6H, m), 4.96 (2H, app s), 4.78 (1H, m), 4.73 (1H, m), 4.36 (1H, d, J = 10.2 Hz), 4.22 (1H, d, J = 10.2 Hz), 3.37 (2H, app s), 2.91 (1H, dd, J = 16.6, 6.4 Hz), 2.62 (1H, dd, J = 16.6, 5.9 Hz), 2.12 (1H, m), 1.00 (3H, d, J = 6.3 Hz), 0.87 93H, d, J = 6.3 Hz): MS $[M+Na]^+$ 674

From more polar t-butyl ester: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 (1H, d, J = 8.3 Hz), 8.79 (1H, d, J = 8.8 Hz), 8.43 (1H, s), 8.00-7.80 (4H, m), 7.61 (2H, m), 7.23-7.17 94H, m), 6.93-6.77 (6H, m), 4.99 (1H,

d, J = 17.6 Hz), 4.86 (1H, d, J = 18.1 Hz), 4.79 (1H, m), 4.72 (1H, m0, 4.43 (1H, d, J = 10.7 Hz), 4.20 (1H, d, J = 10.2 Hz), 2.81 (1H, dd), 2.56 (1H, dd), 2.17 (1H, m), 1.01 (3H, d, J = 6.3 Hz), 0.99 (3H, d, J = 6.3 Hz): MS $[M+Na]^+$ 674

· (3S)-3-{3-[(1S)-1-(naphthalene-1-carbonylamino)-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (compound 27)

From less polar t-butyl ester: ^1H NMR (500 MHz, DMSO-d_6) δ 9.08 (1H, d, J = 7.8 Hz), 8.87 (1H, d, J = 8.8 Hz), 8.55 (1H, s), 8.10-8.01 (4H, m), 7.68 7.58 (5H, m), 7.26 (2H, t, J = 7.8 Hz), 6.98-6.92 (3H, m), 5.27 (2H, ABq, J = 16.6 Hz0, 4.82-4.78 (2H, m), 4.43 (1H, d, J = 10.7 Hz), 4.29 (1H, d, J = 10. 3 Hz), 3.44 (2H, ABq, J = 18.1 Hz), 3.01 (1H, dd, J = 17.1, 6.4 Hz), 2.67 (1H, dd, J = 17.1, 6.3 Hz), 2.21 (1H, m), 1.07 (3H, d, J = 6.2 Hz), 0.97 (3H, d, J = 6.2 Hz): MS $[M+Na]^+$ 770

From more polar t-butyl ester: ^1H NMR (500 MHz, DMSO-d_6) δ 8.97 (1H, d, J = 7.8 Hz), 8.85 (1H, d, J = 8.3 hz), 8.50 (1H, s), 8.09-7.96 (4H, m), 7.67-7.60 (5H, m), 7.32 (2H, t, J = 6.3 Hz), 7.00 (3H, m), 5.38 (1H, d, J = 17.1 Hz), 5.13 (1H, d, J = 17.1 Hz), 4.92 (1H, d, J = 6.3 Hz), 4.79 (1H, t, J = 7.8 Hz), 4.55 (1H, d, J = 9.7 Hz), 4.28 (1H, d, J = 8.7 Hz), 3.48 (1H, d, J = 18.1 Hz), 3.38 (1H, d, J = 18.1 Hz), 2.87 (1H, dd, J = 17.1, 4.9 Hz), 2.60 (1H, dd, J = 17.1, 4.9 Hz), 2.25 (1H, m), 1.07 (6H, m): MS $[M+Na]^+$ 770

· (3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid (compound 23, diastereomeric)

^1H NMR (500 MHz, DMSO-d_6) δ 8.72-8.55 (2H, m), 8.38 (1H, s), 8.04-7.85 (4H, m), 7.62 (2H, m), 7.25-7.12 (7H, m), 6.91-6.70 (3H, m),

4.79-4.51 (4H, m), 3.40-3.05 (4H, m), 2.73-2.23 (2H, m), 2.01 (1H, m), 0.94-0.70 (6H, m): MS $[M+Na]^+$ 658

· (3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (compound 28)

From less polar t-butyl ester: ^1H NMR (500 MHz, DMSO-d_6) δ 8.68 (1H, d, J = 8.8 Hz), 8.59 (1H, d, J = 8.3 Hz), 8.40 (1H, s), 8.05-7.87 (4H, m), 7.63-7.54 (5H, m), 7.21-7.13 (5H, m), 5.98 (2H, ABq, J = 17.1 Hz), 4.74 (1H, m), 4.64 (1H, m), 3.25-3.10 (4H, m), 2.62 (1H, dd, J = 17.1, 6.3 Hz), 2.37 (1H, dd, J = 16.6, 5.4 Hz), 2.06 (1H, m), 0.93 (3H, d, J = 6.8 Hz), 0.83 (3H, d, J = 6.2 Hz): MS $[M+Na]^+$ 754

From more polar t-butyl ester: ^1H NMR (500 MHz, DMSO-d_6) δ 8.72 (1H, d, J = 8.3 Hz), 8.59 91H, d, J = 8.8 Hz), 8.41 (1H, s), 8.01-7.87 (4H, m), 7.62-7.53 (5H, m), 7.29-7.21 (5H, m), 4.70-4.55 (4H, m), 3.44-3.10 (4H, m), 2.72-2.67 (1H, dd, J = 16.6, 7.3 Hz), 2.38-2.34 (1H, dd, J = 16.6, 7.3 Hz), 2.05 (1H, m), 0.97 (3H, d, J = 6.3 Hz), 0.79 (3H, d, J = 6.3 Hz); MS $[M+Na]^+$ 754.

· (3S)-3-{3-[(1S)-1-(quinoline-2-yl-carbonylamino)-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid (compound 22, diastereomeric mixture)

^1H NMR (500 MHz, DMSO-d_6) δ 9.06 (1H, m), 8.82 91H, br), 8.57 (1H, m), 8.16-7.74 95H, m), 7.26-7.12 (4H, m), 6.89-6.69 (6H, m), 5.10-4.70 (4H, m), 4.48-4.20 (2H, m), 2.87-2.53 (2H, m), 2.32 (1H, m), 0.98-0.85 (6H, m): MS $[M+Na]^+$ 675, $[M+H]^+$ 653.

· (3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2-naphthyloxy)-pent

anoic acid (compound 25)

From less polar t-butyl ester: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.96 (1H, d, J = 7.8 Hz), 8.77 (1H, d, J = 8.3 Hz), 8.47 (1H, s), 8.03-7.57 (9H, m), 7.44 (1H, t, J = 6.8 Hz), 7.34 (1H, t, J = 7.8 Hz), 7.17-7.13 (4H, m), 6.88-6.82 (3H, m), 5.09 (2H, ABq), 4.84 (1H, m), 4.72 (1H, m), 4.38 (1H, d, J = 10.2 Hz), 4.23 (1H, d, J = 10.7 Hz), 2.94 (1H, dd, J = 17.1, 6.8 Hz), 2.65 (1H, dd, J = 16.6, 5.9 Hz), 2.12 (1H, m), 0.97 (3H, d, J = 6.3 Hz), 0.85 (3H, d, J = 6.3 Hz): MS $[M+Na]^+$ 724

From more polar t-butyl ester: ^{1}H NMR (50°C, 300 MHz, DMSO-d_6) δ 8.72 (1H, d), 8.63 (1H, d), 8.41 (1H, s), 7.94-6.72 (19H, m), 5.03 (2H, ABq), 4.88 (1H, m), 4.74 (1H, m), 4.42 91H, d), 4.19 (1H, m), 3.38 (2H, ABq), 2.88 (1H, dd), 2.65 (1H, dd), 2.19 (1H, m), 1.02 (6H, two d):MS $[M+Na]^+$ 724

^{13}C NMR (50°C, 300 MHz, DMSO-d_6) δ 202.1, 171.6, 170.7, 166.6, 159.3, 158.0, 155.6, 134.1, 133.9, 132.0, 131.6, 129.3, 129.1, 128.7, 127.7, 127.5, 127.3, 126.5, 126.2, 124.2, 123.6, 121.1, 118.1, 114.5, 107.4, 87.5, 70.2, 52.9, 34.4, 29.6, 19.4, 18.9.

More polar diastereomer's methyl ester: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (1H, s), 8.02-6.68 (20H, m), 5.09-4.95 (2H, ABq, J = 16.6 Hz), 5.10 (1H, m), 5.01(1H, m), 4.34 (2H, ABq, J = 10.3 Hz), 3.70 (3H, s), 3.50-3.33 (2H, ABq, J = 17.6 Hz), 3.13 (1H, dd, J = 17.1, 4.9 Hz), 2.90 (1H, dd, J = 17.1, 5.9 Hz), 2.23 (1H, m), 1.08 and 1.02 (6H, two d, J = 6.8 Hz).

· (3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(1-naphthyloxy)-pentanoic acid (compound 24, diasteromeric mixture)

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.02-8.18(3H, m), 8.05-6.80 (18H, m), 5.15-4.15 (6H, m), 2.90-2.55 (2H, m), 2.14 (1H, m), 1.05-0.82 (6H, m).

· (3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2-naphthyloxy)-pentanoic acid (compound 29, diasteromeric mixture)

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.95-8.46 (3H, m), 8.09-7.07 (13H, m), 5.21-4.75 (5H, m), 2.95-2.64 (2H, m), 2.19 (1H, m): MS $[M+H]^+$ 596

· (3S)-3-{3-[2-methyl-(1S)-1-(2-naphthalenecarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (compound 30, diasteromeric mixture)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.76-8.69 (m, 2H), 8.45 (m, 1H), 8.04-7.90 (m, 5H), 7.61 (m, 2H), 7.31-7.19 (m, 2H), 6.97-6.81 (m, 3H), 5.09-4.68 (m, 5H), ~3.3 (m, 2H), 2.82 (m, 1H), 2.64 (m, 1H), 2.15 ((m, 1H), 1.00-0.84 (m, 6H): MS [M+Na] = 568

· (3S)-3-{3-[2-methyl-(1S)-1-(phenylethylcarbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (compound 32, diastereomeric mixture)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.48 (br s, 1H), 8.00 (m, 1H), 7.61-7.54 (m, 3H), 7.30-7.15 (m, 11H), 4.93-4.32 (m, 4H), 3.34-2.90 (m, 4H), 2.78 (m, 1H), 1.78 (m, 1H), 0.90-0.60 (m, 6H): MS [M+Na] = 732

· (3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenecarbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid(compound 33)

From more polar t-butyl ester: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.80 (d, J = 8.3 Hz, 1H), 8.63 (d, J = 7.8 Hz, 1H), 8.02 (m, 3H), 7.64-7.20 (m, 12H), 4.81-4.55 (m, 4H), 3.39 (m, 2H), 3.12 (m, 2H), 2.73 (m, 1H),

2.43 (m, 1H), 1.98 (m, 1H), 0.99 (d, J = 4.6 Hz, 3H), 0.79 (d, J = 4.5 Hz, 3H): MS [M+Na] = 754

From less polar t-butyl ester: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.77 (d, J = 8.7 Hz, 1H), 8.62 (d, J = 8.3 Hz, 1H), 8.08-7.97 (m, 4H), 7.61-7.21 (m, 12H), 5.00 (m, 2H), 4.77-4.67 (m, 2H), 3.39-3.27 (m, 2H), 3.15-3.11 (m, 2H), 2.64 (m, 1H), 2.40 (m, 1H), 1.99 (m, 1H), 0.96 (d, J = 6.4 Hz, 3H), 0.85 (d, J = 6.9 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(cinnamoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (compound 38)

Fom more polar t-butyl ester: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.55 (d, J = 8.7 Hz, 1H), 8.28 (d, J = 8.7 Hz, 1H), 7.60-7.19 (m, 14H), 6.70 (d, J = 15.6 Hz, 1H), 4.71-4.49 (m, 4H), ~3.3 (m, 2H), 3.08 (m, 2H), 2.71 (m, 1H), 2.40 (m, 1H), 1.90 (m, 1H), 0.86 (d, J = 6.4 Hz, 3H), 0.74 (d, J = 6.4 Hz, 3H): MS [M+H] = 708

From less polar t-butyl ester: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.53 (d, J = 8.3 Hz, 1H), 8.28 (d, J = 8.7 Hz, 1H), 7.61-7.16 (m, 14H), 6.69 (d, J = 16.9 Hz, 1H), 4.99-4.92 (ABq, J = 17.4 Hz, 2H), 4.72 (m, 1H), 4.53 (m, 1H), 3.36 (d, J = 17.9 Hz, 1H), 3.23 (d, J = 13.8 Hz, 1H), 3.10-3.04 (m, 2H), 2.61 (dd, J = 17.0, 6.4 Hz, 1H), 2.37 (dd, J = 17.0, 6.0 Hz, 1H), 1.90 (m, 1H), 0.79 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(phenylmethylsulfonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (compound 39, diastereomeric)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 7.75 and 7.69 (m, 1H), 7.61-7.13 (m, 13H), 5.00 and 4.70 (m, 1H), 4.64 (m, 2H), 4.22-3.78 (m, 4H), 1.79 (m, 1H), 0.90 (m, 6H):MS [M+H] = 732.

· (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (compound 40)

From more polar isomer: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.94 (d, J = 9.7 Hz, 1H), 8.75 (d, J = 7.8 Hz, 1H), 8.55 (d, J = 8.8 Hz, 1H), 8.18-8.05 (m, 3H), 7.85 (m, 1H), 7.55 (m, 3H), 5.22-5.06 (m, 3H), 4.83-4.70 (m, 2H), 3.35 (m, 2H), 2.80 (m, 1H), 2.61 (m, 1H), 2.31 (m, 1H), 0.95 (m, 6H):MS [M+H] = 643

From less polar isomer: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.07 (d, J = 9.2 Hz, 1H), 8.76 (d, J = 8.3 Hz, 1H), 8.56 (d, J = 8.7 Hz, 1H), 8.20-8.07 (m, 3H), 7.87 (m, 1H), 7.72 (m, 1H), 7.62-7.54 (m, 3H), 5.21-5.06 (m, 3H), 4.84-4.70 (m, 2H), 3.44-3.27 (m, 2H), 2.85 (dd, J = 17.0, 6.0, 1H), 2.66 (dd, J = 17.0, 6.9 Hz, 1H), 2.29 (m, 1H), 0.98 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.4 Hz, 6H)

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (compound 41)

From more polar isomer: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.95 (d, 1H), 8.72 (d, 1H), 8.55 (d, 1H), 8.20-8.05 (m, 3H), 7.86 (m, 1H), 7.72 (m, 1H), 7.24-6.74 (m, 5H), 5.11-4.70 (m, 5H), 3.34 (m, 2H), 2.80 (m, 1H), 2.62 (m, 1H), 2.30 (m, 1H), 0.95 (m, 6H):MS [M+H] = 547

From less polar isomer: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.03 (d, 1H), 8.74 (d, 1H), 8.56 (d, 1H), 8.20-8.07 (m, 3H), 7.87 (m, 1H), 7.73 (m, 1H), 7.23 (m, 2H), 6.88 (m, 3H), 5.09-4.71 (m, 5H), 3.34 (m, 2H), 2.85 (m, 1H), 2.65 (m, 1H), 2.27 (m, 1H), 0.96-0.87 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoylo

xy)-pentanoic acid (compound 42)

From more polar isomer: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.91 (d, J = 9.2 Hz, 1H), 8.59-8.52 (m, 2H), 8.17-8.06 (m, 3H), 7.87 (m, 1H), 7.72 (m, 1H), 7.58-7.53 (m, 5H), 4.69-4.51 (m, 4H), 3.40 (m, 2H), 3.16 (m, 1H), 2.69 (m, 1H), 2.37 (m, 1H), 2.19 (m, 1H), 0.91-0.80 (m, 6H): MS [M+H] = 733

From less polar isomer: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.92 (d, J = 9.2 Hz, 1H), 8.56(m, 2H), 8.19-8.07 (m, 3H), 7.87 (m, 1H), 7.73 (m, 1H), 7.60-7.54 (m, 3H), 7.22-7.07 (m, 5H), 5.01-4.93 (ABq, J = 16.5 Hz, 2H), 4.75-4.62 (m, 2H), 3.46 (d, J = 18.4 Hz, 1H), 3.23-3.07 (m, 3H), 2.62 (dd, J = 17.0, 6.9 Hz, 1H), 2.37 (dd, J = 17.0, 6.0 Hz, 1H), 2.21 (m, 1H), 0.86-0.83 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (compound 43)

From more polar isomer: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.91 (d, J = 9.2 Hz, 1H), 8.62 (d, J = 8.3 Hz, 1H), 8.52 (d, J = 8.7 Hz, 1H), 8.15 (d, J = 8.3 Hz, 1H), 8.07 (m, 2H), 7.86 (m, 1H), 7.72 (m, 1H), 7.26-7.09 (m, 7H), 6.86 (m, 1H), 6.69 (d, J = 8.3 Hz, 2H), 4.71-4.63 (m, 2H), 4.54-4.46 (ABq, J = 17.9 Hz, 2H), 3.42 (d, J = 17.9 Hz, 1H), 3.29 (d, J = 13.8 Hz, 1H), 3.15 (d, J = 18.4 Hz, 1H), 3.09 (d, J = 14.3 Hz, 1H), 2.72 (dd, J = 17.0, 6.9 Hz, 1H), 2.36 (dd, J = 17.0, 6.0 Hz, 1H), 2.15 (m, 1H), 0.88 (d, J = 6.9 Hz, 3H), 0.75 (d, J = 6.9 Hz, 3H): MS [M+H] = 637

From less polar isomer: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.88 (d, J = 9.6 Hz, 1H), 8.54 (m, 2H), 8.18-8.06 (m, 3H), 7.87 (m, 1H), 7.72 (m, 1H), 7.28-6.78 (m, 10H), 4.78-4.63 (m, 4H), 3.45 (d, J = 18.3 Hz, 1H), 3.26-3.06 (m, 3H), 2.66-2.62 (dd, J = 17.0, 6.9 Hz, 1H), 2.44-2.39 (dd, J

= 17.0, 5.5 Hz, 1H), 2.17 (m, 1H), 0.80 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-(1-imid azolylmethyl)-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-penta noic acid (compound 44, diastereomeric mixture)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.09-6.60 (m, 16H), 4.92-4.62 (m, 6H), 3.50 (m, 2H), 2.85-2.20 (m, 3H), 0.93 (m, 6H): MS [M+H] = 627

· (3S)-3-{3-[2-methyl-(1S)-1-(2-naphthalenecarbonylamino)-propyl]-4,5-dihydr o-isoxazole-5-carbonylamino}-4-keto-pentanoic acid (compound 45, diastereomeric mixture)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.77 (m.1H), 8.45 (m, 2H), 8.07-7.89 (m, 4H), 7.61 (m, 2H), 5.06 (m, 1H), 4.72 (m, 1H), 4.46 & 4.38 (two m, 1H), ~3.3 (m, isoxazoline CH_2), 2.62 (m, 1H), ~2.49 (m, 1H), 2.13 (m, 1H), 2.09 & 2.05 (two s, 3H), 1.01-0.84 (m, 6H).

· (3S)-3-{3-[(1S)-1-(succinoylamino)-3-carboxy-propyl]-5-methyl-4,5-dihydro-i soxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (compound 46, diastereomeric mixture)

^{1}H-NMR (500 MHz,DMSO-d_6) δ 8.56-8.52 (m, 1H), 8.15 (m, 1H), 7.27 (m, 2H), 6.97-6.82 (m, 3H), 4.96-4.83 (m, 2H), 4.77 (m, 1H), 4.58 (m, 1H), 3.58-2.22 (m, 10H), 2.0-1.74 (m, 2H), 1.47 & 1.45 (two s, 3H):MS [M+Na] = 558.

· (3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-is oxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (compound 47, diastereomeric mixture)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.62-8.52 (m, 1H), 8.06 (m, 1H), 7.27 (m, 2H), 6.96-6.81 (m, 3H), 4.94-4.72 (m, 3H), 4.43-4.32 (m, 1H),

3.38-3.22 (m, 1H), 2.94-2.78 (m, 2H), 2.70-2.22 (m, 5H), 1.95-1.77 (m, 1H), 1.48 & 1.46 (two s, 3H), 0.86-0.70 (m, 6H): MS [M+Na] = 528.

· (3S)-3-{3-[2-methyl-(1S)-1-(1-naphtalenylcarbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(1-piperidinyl)-pentanoic acid (compound 48, diastereomeric)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.75 (m, 1H), 8.47 and 8.29 (m, 1H), 8.03-7.23 (m, 12H), 4.65 (m, 2H), 3.11-2.99 (m, 2H), 2.26-2.18 (m, 4H), 1.97 (m, 1H), 1.64-0.79 (m, 12H):MS [M+H] = 627.

· (3S)-3-{3-[2-methyl-(1S)-1-(isoquinoline-1-carbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 49LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.03 (d, J = 9.2 Hz, 1H), 8.74 (d, J = 8.3 Hz, 1H), 8.60-8.56 (m, 2H), 8.07-8.03 (m, 2H), 7.83 (m, 1H), 7.73 (m, 1H), 7.61-7.53 (m, 3H), 7.22-7.17 (m, 5H), 5.01-4.93 (ABq, J = 17.0 Hz, 2H), 4.74-4.63 (m, 2H), 3.41 (d, J = 17.9 Hz, 1H), 3.23 (d, J = 14.2 Hz, 1H), 3.13 (d, J = 17,9 Hz, 1H), 3.09 (d, J = 14.2 Hz, 1H), 2.60 (m, 1H), 2.36 (m, 1H), 2.10 (m, 1H), 0.91 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.4 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(isoquinoline-1-carbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 50LP: stereoisomer of 49LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.04 (d, J = 9.2 Hz, 1H), 8.65-8.60 (m, 2H), 8.53 (d, J = 6.0 Hz, 1H), 8.05-8.00 (m, 2H), 7.82 (m, 1H), 7.72 (m, 1H), 7.60-7.53 (m, 3H), 7.30-7.17 (m, 5H), 4.75-4.53 (m, 4H), 3.5-3.3 (m, 2H, buried under solvent peaks), 3.13 (m, 2H), 2.68 (m, 1H), 2.41 (m, 1H), 2.04 (m, 1H), 0.95 (d, J = 6.4 Hz, 3H), 0.78 (d, J = 6.4 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(isoquinoline-3-carbonylamino)-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 51LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.40 (s, 1H), 8.99 (d, J = 9.2 Hz, 1H), 8.56 (m, 2H), 8.26 (d, J = 7.8 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 7.90-7.81 (m, 2H), 7.60-7.53 (m, 3H), 7.20-7.07 (m, 5H), 5.01-4.92 (ABq, J = 17.0 Hz, 2H), 4.73-4.66 (m, 2H), ~3.4 (m, 1H, buried under solvent peaks), 3.23-3.05 (m, 3H), 2.60 (m, 1H), 2.34 (m, 1H), 2.19 (m, 1H), 0.82 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(isoquinoline-3-carbonylamino)-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid(Compound 52MP: stereoisomer of Compound 51)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.39 (s, 1H), 8.97 (d, J = 9.6 Hz, 1H), 8.58 (d, J = 8.7 Hz, 1H), 8.53 (s, 1H), 8.24 (d, J = 8.3 Hz, 1H), 8.13 (d, J = 7.8 Hz, 1H), 7.88-7.81 (m, 2H), 7.58-7.53 (m, 3H), 7.27-7.18 (m, 5H), 4.72-4.49 (m, 4H), 3.6-3.3 (m, 2H, buried under solvent peaks), 3.19-3.08 (m, 2H), 2.67 (m, 1H), 2.34 (m, 1H), 2.18 (m, 1H), 0.87 (d, J = 6.9 Hz, 3H), 0.78 (d, J = 6.9 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(isoquinoline-4-carbonylamino)-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 53 LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.02 (m, 2H), 8.63 (d, J = 8.7 Hz, 1H), 8.10 (d, J = 8.3 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.83 (m, 1H), 7.69 (m, 1H), 7.61-7.53 (m, 3H), 7.44 (d, J = 4.2 Hz, 1H), 7.31-7.20 (m, 6H), 4.98 (m, 2H), 4.76-4.65 (m, 2H), 3.37 (d, J = 17.9 Hz, 1H), 3.29 (d, J = 14.2 Hz, 1H), 3.15-3.11 (m, 2H), 2.63 (m, 1H), 2.39 (m, 1H), 1.99

(m, 1H), 0.93 (d, J = 6.9 Hz, 3H), 0.85 (d, J = 6.9 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(isoquinoline-4-carbonylamino)-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoylo xy)-pentanoic acid (Compound 54 MP: stereoisomer of Compound 53 LP)
^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.05 (d, J = 8.7 Hz, 1H), 8.96 (d, J = 4.1 Hz, 1H), 8.64 (d, J = 8.7 Hz, 1H), 8.08 (d, J = 8.3 Hz, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.82 (m, 1H), 7.69-7.48 (m, 5H), 7.31-7.20 (m, 5H), 4.80-4.55 (m, 4H), 3.6-3.3 (m, 2H, buried under solvent peaks), 3.14-3.09 (m, 2H), 2.72 (m, 1H), 2.41 (m, 1H), 1.95 (m, 1H), 0.96 (d, J = 6.9 Hz, 3H), 0.78 (d, J = 6.9 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(benzofuran-2-carbonylamino)-propyl]-5-phenylm ethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 55LP)
^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.83 (d, J = 9.2 Hz, 1H), 8.56 (d, J = 8.3 Hz, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.61-7.33 (m, 6H), 7.20-7.04 (m, 5H), 5.00-4.92 (m, 2H), 4.73 (m, 1H), 4.56 (m, 1H), ~3.37 (m, 1H), 3.23-3.05 (m, 3H), 2.61 (m, 1H), 2.36 (m, 1H), 2.08 (m, 1H), 0.88-0.78 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(benzofuran-2-carbonylamino)-propyl]-5-phenylm ethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 56: stereoisomer of Compound 55LP)
^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.83 (d, J = 9.2 Hz, 1H), 8.55 (d, J = 8.7 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.58-7.43 (m, 5H), 7.33-7.18 (m, 6H), 4.69-4.55 (m, 4H), 3.43-3.30 (m, 2H), 3.12-3.07 (m, 2H), 2.69 (m, 1H), 2.37 (m, 1H), 2.06 (m, 1H), 0.90 (d, J = 6.4 Hz, 3H), 0.74 (d, J = 6.4 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-1-carbonylamino)-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-difluorobenzoylo xy)-pentanoic acid (Compound 57LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.77 (d, J = 9.7 Hz, 1H), 8.64 (d, J = 8.3 Hz, 1H), 8.06-7.95 (m, 3H), 7.69-7.44 (m, 5H), 7.26 (m, 7H), 5.02-4.90 (ABq, J = 17.0 Hz, 2H), 4.71 (m, 2H), 3.30-3.10 (m, 4H), 2.65 (m, 1H), 2.39 (m, 1H), 1.99 (m, 1H), 0.94 (d, J = 6.0 Hz, 3H), 0.84 (d, J = 6.0 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-1-carbonylamino)-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dimethylbenzoylo xy)-pentanoic acid(Compound 61: diastereomeric mixture)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.82-8.76 (m, 1H), 8.65 (m, 1H), 8.08-7.95 (m, 3H), 7.59-7.46 (m, 4H), 7.33-7.06 (m, 8H), 4.98-4.49 (m, 4H), 3.42-3.09 (m, 4H), 2.76-2.39 (m, 2H), 2.28 & 2.25 (two s, 6H), 1.98 (m, 1H), 0.99-0.76 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-8-carbonylamino)-propyl]-5-phenylmet hyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 62: diastereomeric mixture)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 11.19-11.08 (m, 1H), 9.04 (m, 1H), 8.65-8.50 (m, 3H), 8.22 (m, 1H), 7.80-7.51 (m, 5H), 7.30-7.06 (m, 5H), 5.00-4.47 (m, 4H), 3.46-3.02 (m, 4H), 2.73-2.34 (m, 2H), 2.11 (m, 1H), 1.00-0.80 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(indole-2-carbonylamino)-propyl]-5-phenylmethyl -4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pe ntanoic acid(Compound 63LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 11.58 (s, 1H), 8.56 (d, J = 8.7 Hz, 1H), 8.49 (d, J = 8.7 Hz, 1H), 7.64-7.53 (m, 4H), 7.43 (d, J = 8.3 Hz, 1H), 7.24-7.03 (m, 8H), 5.00-4.92 (ABq, J = 17.0 Hz, 2H), 4.74-4.56 (m, 2H), ~3.5 (m, 1H, buried under solvent peaks), 3.23 (d, J = 13.8 Hz, 1H), 3.15-3.06 (m, 2H), 2.60 (m, 1H), 2.35 (m, 1H), 2.02 (m, 1H), 0.90 (d, J = 6.4 Hz, 3H), 0.81 (d, J = 6.9 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(indole-2-carbonylamino)-propyl]-5-phenylmethyl -4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pe ntanoic acid (Compound 64MP: stereoisomer of Compound 63LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 11.56 (s, 1H), 8.54 (m, 2H), 7.60-7.02 (m, 13H) 4.71-4.51 (m, 4H), , 3.41-3.31 (m, 2H), 3.15-3.07 (m, 2H), 2.67 (m, 1H), 2.38 (m, 1H), 2.05 (m, 1H), 0.92 (d, J = 6.9 Hz, 3H), 0.77 (d, J = 6.9 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(indole-3-carbonylamino)-propyl]-5-phenylmethyl -4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pe ntanoic acid (Compound 65LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 11.61 (s, 1H), 8.56 (d, J = 8.3 Hz, 1H), 8.08 (m, 2H), 7.91 (d, J = 9.2 Hz, 1H), 7.62-7.54 (m, 3H), 7.43 (d, J = 8.3 Hz, 1H), 7.22-7.00 (m, 7H), 4.95 (m, 2H), 4.72-4.61 (m, 2H), ~3.4 (m, 1H, buried under solvent peaks), 3.23 (d, J = 13.8 Hz, 1H), 3.13-3.06 (m, 2H), 2.61 (m, 2H), 2.34 (m, 1H), 1.99 (m, 1H), 0.91 (d, J = 6.4 Hz, 3H), 0.81 (d, J = 6.4 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(indole-3-carbonylamino)-propyl]-5-phenylmethyl -4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pe ntanoic acid (Compound 66MP: stereoisomer of Compound 65LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 11.60 (s, 1H), 8.54 (d, J = 8.7 Hz,

1H), 8.11-8.06 (m, 2H), 7.91 (d, J = 9.2 Hz, 1H), 7.60-7.05 (m, 11H), 4.71-4.47 (m, 4H), 3.33 (m, 2H), 3.09 (m, 2H), 2.68 (m, 2H), 2.39 (m, 1H), 2.00 (m, 1H), 0.93 (d, J = 6.4 Hz, 3H), 0.78 (d, J = 6.9 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-1-carbonylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 67LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.86 (d, J = 9.2 Hz, 1H), 8.73 (d, J = 8.3 Hz, 1H), 8.11-7.98 (m, 3H), 7.64-7.54 (m, 7H), 5.17-5.08 (ABq, J = 17.0 Hz, 2H), 4.81-4.70 (m, 2H), ~3.4 (m, 1H, buried under solvent peaks), 3.05 (d, J = 17.9 Hz, 1H), 2.87 (m, 1H), 2.65 (m, 1H), 2.02 (m, 1H), 1.55 (s, 3H), 1.00 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-1-carbonylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 68MP: stereoisomer of Compound 67LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.84 (d, J = 8.7 Hz, 1H), 8.69 (d, J = 8.3 Hz, 1H), 8.06-7.96 (m, 3H), 7.62-7.52 (m, 7H), 5.23-5.11 (ABq, J = 17.0 Hz, 2H), 4.82-4.67 (m, 2H), 3.6-3.4 (m, 1H, buried under solvent peaks), 3.00 (d, J = 17.9 Hz, 1H), 2.82 (m, 1H), 2.58 (m, 1H), 2.05 (m, 1H), 1.56 (s, 3H), 1.01-0.93 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(benzofuran-2-carbonylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 69LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.91 (d, J = 8.7 Hz, 1H), 8.70 (d, J = 8.2 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.62-7.54 (m, 4H), 7.48 (m, 1H), 7.34 (m, 1H), 5.16-5.07 (ABq, J = 17.0 Hz, 2H), 4.79 (m, 1H), 4.61 (m, 1H), 3.44 (d, J = 17.9 Hz, 1H), 3.02 (d,

J = 17.9 Hz, 1H), 2.87 (dd, J = 17.0, 6.0 Hz, 1H), 2.65 (dd, J = 17.0, 7.4 Hz, 1H), 2.11 (m, 1H), 1.50 (s, 3H), 0.94 (d, J = 6.9 Hz, 3H), 0.83 (d, J = 6.4 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(benzofuran-2-carbonylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 70MP: stereoisomer of Compound 69LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.86 (d, J = 8.7 Hz, 1H), 8.62 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.65 (d, J = 8.3 Hz, 1H), 7.60-7.52 (m, 4H), 7.45 (m, 1H), 7.31 (m, 1H), 5.14-5.07 (ABq, J = 17.0 Hz, 2H), 4.71 (m, 1H), 4.62 (m, 1H), 3.44 (d, J = 17.9 Hz, 1H), 3.00 (d, J = 17.9 Hz, 1H), 2.79 (dd, J = 17.0, 6.4 Hz, 1H), 2.56 (dd, J = 17.0, 6.0 Hz, 1H), 2.16 (m, 1H), 1.53 (s, 3H), 0.95-0.91 (m, 6H).

· (3S)-3-{3-[3-carboxy-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid(Compound 71LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.60 (d, J = 8.3 Hz, 1H), 8.15 (d, J = 8.3 Hz, 1H), 7.61-7.54 (m, 3H), 5.16-5.08 (ABq, J = 17.0 Hz, 2H), 4.78 (m, 1H), 4.62 (m, 1H), 3.31 (d, J = 17.9 Hz, 1H), 2.90 (d, J = 17.9 Hz, 1H), 2.85 (dd, J = 17.0, 6.0 Hz, 1H), 2.64 (dd, J = 17.0, 6.9 Hz, 1H), 2.44 (m, 2H), 2.33 (m, 2H), 2.24 (m, 2H), 1.90-1.76 (m, 2H), 1.46 (s, 3H).

· (3S)-3-{3-[3-carboxy-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid(Compound 72MP: stereoisomer of Compound 71LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.55 (d, J = 8.3 Hz, 1H), 8.16 (d, J = 8.3 Hz, 1H), 7.62-7.55 (m, 3H), 5.21-5.09 (ABq, J = 17.0 Hz, 2H), 4.76

(m, 1H), 4.58 (m, 1H), 3.23 (d, J = 17.9 Hz, 1H), 2.95 (d, J = 17.9 Hz, 1H), 2.83 (dd, J = 17.0, 6.5 Hz, 1H), 2.62 (dd, J = 17.0, 6.4 Hz, 1H), 2.44 (m, 2H), 2.33 (m, 2H), 2.25 (m, 2H), 1.96 (m, 1H), 1.80 (m, 1H), 1.50 (s, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid(Compound 73LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.66 (d, J = 8.3 Hz, 1H), 8.10 (d, J = 8.7 Hz, 1H), 7.62-7.57 (m, 3H), 5.14-5.05 (ABq, J = 17.0 Hz, 2H), 4.77 (m, 1H), 4.36 (m, 1H), 3.31 (d, J = 18.4 Hz, 1H), 2.92 (d, J = 18.4 Hz, 1H), 2.87-2.83 (m, 1H), 2.66-2.61 (m, 1H), 2.44 (m, 1H), 2.37 (m, 1H), 1.84 (m, 1H), 1.48 (s, 3H), 0.87 (d, J = 6.4 Hz, 3H), 0.77 (d, J = 6.4 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid(Compound 74MP: stereoisomer of Compound 73LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.56 (d, J = 8.3 Hz, 1H), 8.08 (d, J = 8.7 Hz, 1H), 7.62-7.57 (m, 3H), 5.19-5.08 (ABq, J = 17.0 Hz, 2H), 4.75 (m, 1H), 4.40 (m, 1H), 3.30 (d, J = 17.9 Hz, 1H), 2.93 (d, J = 17.9 Hz, 1H), 2.82 (m, 1H), 2.60 (m, 1H), 2.44-2.31 (m, 4H), 1.92 (m, 1H), 1.51 (s, 3H), 0.86-0.84 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-propyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid(Compound 75LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.64 (d, J = 8.3 Hz, 1H), 8.09 (d, J = 8.7 Hz, 1H), 7.60 (m, 3H), 5.17-5.04 (ABq, J = 17.0 Hz, 2H), 4.83 (m,